BRAIN.

PART I., 1900.

Original Articles and Clinical Cases.

ON THE EXCITABILITY OF NERVOUS MATTER, WITH ESPECIAL REFERENCE TO THE RETINA.[1]

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I HAVE not failed to pass through the preparatory searchings of mind incidental to the delivery of a presidential address, nor to sacrifice to custom by the deliberate writing of a bulky manuscript heavily charged with midnight reflections. But one outcome of those reflections has been an intimate conviction that such deliberate writing is fitted only for the deliberate reading of the fireside, and that it would be impossible for me, within reasonable limits of time, to make my meaning fully clear, by reason of the detail in which it has become enveloped. I have therefore thought preferable to cut myself adrift from the manifold detail of written thought, and endeavour, however lamely and ungrammatically, to at least indicate to you what are the chief new facts that I am selecting to lay before you, and what is the vein of sense which to my mind renders them of neurological value.

[1] Presidential Address to the Neurological Society, February 8, 1900.

My contribution to our common theme is coloured from the laboratory—which, however, will not be accounted to me for unrighteousness in a Society whose distinguishing characteristic it is that it forms a meeting place of complementary interests—from the domain of the laboratory as well as from the hospital—the two chief colours, so to speak, that together make for the neurologist the white light of his knowledge. Nor—to continue the analogy—shall I be unmindful of a third colour by which the triangle of interests is completed in our Society, and I shall try to indicate in the course of my address points of contact with psychological doctrine, of some of the dry facts that belong in first place to physiological analysis.

Let me briefly summarise the subject-matter that I hope to review this evening. I divide it into three chapters, and shall hope under each of these three heads to clearly develop and fix at least one idea of elementary neurological interest.

In Chapter I. I shall briefly refer to a method of procedure, and insist upon the principle that systematic observation of the electrical signs of life yields valuable information.

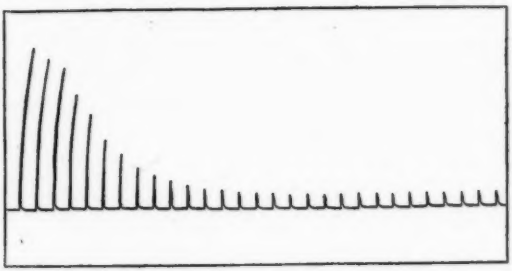
In Chapter II. I shall consider at some length the constructive and disruptive phenomena of which nervous matter is the seat. I shall do this with particular reference to electrical changes produced in the retina by light. I shall briefly describe those changes, and derive from them the conclusion that light excites in the retina a double process of simultaneous decomposition and recomposition; and in conclusion to this chapter I shall take occasion to describe the specific action of protoveratrine upon medullated nerve, viz., an abolition of the positive reaction after action. Incidentally to this matter I shall also refer to the great exhaustibility of non-medullated nerve, and to the slight exhaustibility of the retina as compared with the apparent inexhaustibility of medullated nerve-fibres.

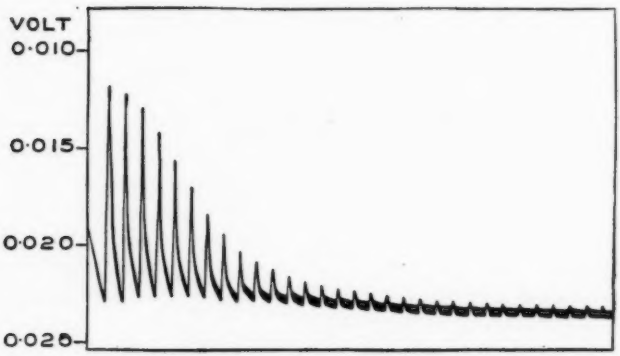
Chapter III. will consist in the consideration of what I term the "law of response," in so far as it can be ascertained by study of the quantitative relations between physical exciting cause and physiological excited effect. My special conclusion *qua* the retina will be:—that the cause-effect curve is an S-shaped or sigmoid curve. My general argument will be:—that a sigmoid curve expresses the ratio between physical stimulus and physiological effect, as well as between physical stimulus and psychological effect.

I.—The Electrical Sign of Life.

Living nervous matter—all living matter indeed—is "excitable" and responds to its "call-from-without" by some form of movement—chemical movement, mechanical movement, electrical movement. An animal gives sign of life by moving. An isolated muscle gives sign of life by contracting when stimulated, and we are able by more or less refined methods to show that such contraction is accompanied by physico-chemical changes—production of acid, evolution of carbon dioxide, rise of temperature, electromotive action. An ordinary nerve, normally connected with its terminal organs, gives sign of life by means of muscle, which by direct or reflex path is set in motion when the nerve-trunk is stimulated. But such nerve separated from its natural termini, isolated from the rest of the organism, gives no sign of life when excited, either in the shape of chemical or of thermic changes, and it is only by means of an electrical change that we can ascertain whether or no it is alive. The eye—the retina—is known to us as a living organ in our own persons when we see an external object. By various devices of the laboratory we measure quantities of stimulant light and differences of excited sensation. The isolated organ—an entire eyeball, or its isolated retina—is best known to be alive or not by means of its electrical response or silence when it is put to the question by its natural stimulus light.

In the three cases named the most general and most delicate sign of life is then the electrical response, and I shall hope to show that the electrical signs of life studied





FIGS. 1 AND 2.

Simultaneous record of a series of muscular contractions and of the corresponding electrical responses.

The muscle (frog's gastrocnemius) connected to an isometric myograph (record A), and led off to a galvanograph (record B), is excited by tetanisation of the sciatic nerve at one minute intervals. Each period of tetanisation lasts six seconds.

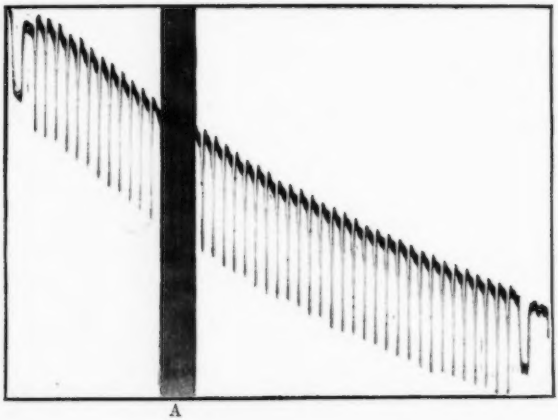
and measured in the laboratory upon these three organs afford very definite contribution to fundamental principles of neurology.

I do not now propose to dwell upon either nerve or muscle. Let me, however—towards establishing in your judgment the general credit of the electrical sign of life—make very brief allusion to experiments upon these two tissues.

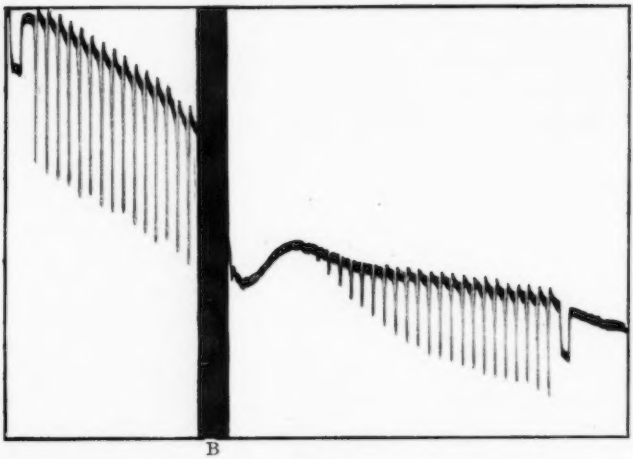
To muscle I shall appeal solely to make good the preliminary position. Compare, *e.g.*, these two simultaneous records—(*a*) of muscular contractions, (*b*) of the electrical responses belonging to the contractions. The electrical effects are to all intents and purposes a replica of the contractions; and if you admit contraction to be valid physiological testimony, you must admit the electrical response to be at least equally valid. The parallelism—as regards fatigue of the end-plate in this case—between the two kinds of record is close, not indeed quite perfect; but of the two versions I should say that the galvanometer gives a rather more faithful report than does the myograph as regards the quantity of chemical change underlying the visible mechanical change.

In the case of nerve, which has no mechanical expression of itself otherwise than by means of muscle, we may, and indeed must, rely upon the galvanometer alone for information as to its physiological state. And nerve—the most hopeless tissue to investigate by way of the indications of muscle, hopeless because nerve is so tough and its terminals are so tender—is an almost ideal sample of living matter upon which to test the comparative effects of all manner of reagents, when the galvanometer is made to be its organ of expression. For we have in our hands a living tissue, absolutely isolated from all other tissues, responding with unfailing regularity so long as nothing more is done to it, and therefore informing us whether or no any given experimental modification affects it. I will content myself by exhibiting to you two typical nerve-records illustrating what I have already on previous occasions at the Society claimed as the distinctive excellence of the method, viz., the clearness of its results. Figs. 3 and 4 are the records of two experiments in which the effects of two gases are tested upon an isolated nerve, their incidence being signalled by the vertical dark

bar. There is no doubtful or obscure result. The gas A had no action. The gas B had an evident action.



A



B

FIGS. 3 AND 4.

Two records of series of electrical responses of nerve, upon which effects of gases are tested. Excitation by tetanisation for 7·5 secs. at one minute intervals. The time during which the nerve is submitted to the influence of the gas is signalled by a vertical dark bar across the record. Gas A is an indifferent gas. Gas B is an anæsthetic gas.

N.B.—The scale in these and other records gives the approximate voltage of deflections.

II.—Constructive and Disruptive Movement.

Let us take as a point of departure "the axiom of general physiology," to which we all subscribe.

Living nervous matter—all living matter—is the seat of two opposite tendencies, integrative and disintegrative, synthetic and analytic, centripetal and centrifugal, constructive and disruptive, anabolic and katabolic, positive and negative. Each act of life is act of death. A muscle by the act of contraction, a nerve-cell by the act of explosion, manifests energy, expends stored matter, undergoes fatigue, and requires to be replenished by the converse act of nutrition. Living tissue, inasmuch as it *is* living, is also dying tissue, ceaselessly evolving energy, ceaselessly "re-storing" energy.

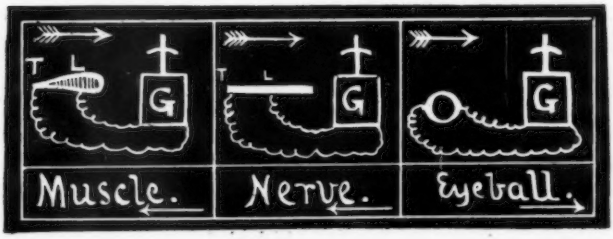


Fig. 5.

To show direction of currents in muscle, nerve, and eyeball. Arrows at top of figure indicate direction of normal current ("current of injury"). Arrows below indicate direction of electrical response to excitation ("current of action").

The double chemical current of which living matter is the centre, manifests itself by actual chemical and structural consequences when it has been sufficiently intense or sufficiently prolonged. Its weakest and briefest pulsations are manifested by electrical changes.

Taking as our line of departure, or zero level, the low-grade continuous chemical change normal in the unexcited state of living tissue—muscle, for example—we have a greater electro-motive action with greater activity of muscle, a lesser electro-motive action with lesser activity. There is

no difference of chemical and electrical state between any two points of an ideally normal uniform muscle—all points are equally alive. If one of the two points be positively active, it will be positively electro-motive. If one of the points be negatively active, it will be negatively electro-motive.

Living muscle—or living nervous matter—or, indeed, any living matter—is excitable, and the most delicate physical sign of that excitability is electromobility, viz., the capacity of manifesting an electrical change in response to excitation. Such electrical change in response to excitation may be positive or negative, positive with augmented disintegration, negative with augmented reintegration.

A muscle, a nerve, an eyeball connected with a galvanometer, as shown in these three sketches, manifests current which we may designate as being upwards (in the tissue) or to the right (through the galvanometer), or positive.

This upward current is due in each case to electromotive action at the point of injury, and gradually subsides—most rapidly in the case of the eyeball, which is apt to exhibit soon after excision a reversed or downward current.

During excitation the upward current undergoes a diminution in the case of muscle or of nerve, an augmentation in the case of the eyeball.

I shall not dwell on the first two cases, they are only presented as affording standards of comparison with the third case, that of the eyeball.

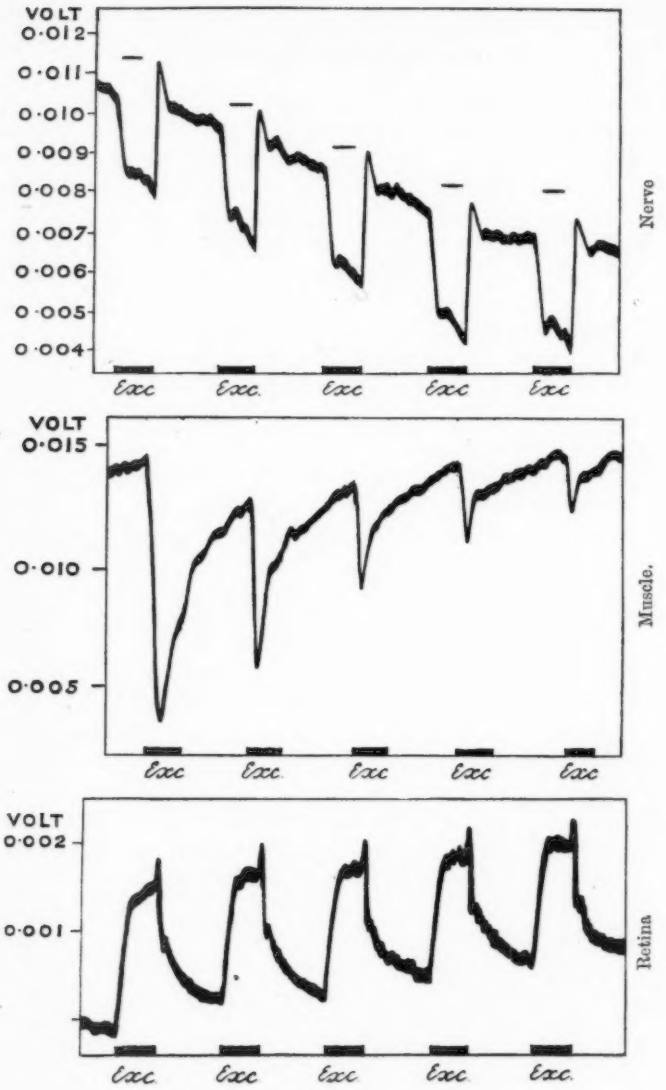
There are two obvious points in the comparison :—

(1) Fatigue, as evidenced by the diminishing maximal effects of a series of maximal excitations, most obvious in the case of muscle, not obvious at all in the case of nerve, is only moderately well marked in the case of the eyeball.

(2) The effects of excitation are negative in the case of muscle and nerve, positive in the case of the eyeball.

Both these points require some comment.

(1) The conditions of observation in the three cases are not strictly identical. In the first two cases the excitation has been electrical, in the third it has been a stimulation by light. I have not yet succeeded in obtaining for comparison



FIGS. 6, 7, AND 8.

Currents of action of nerve, of muscle, and of retina.

In each case the excitation lasts for one minute, and the subsequent period of rest for two minutes. There are five periods of excitation in each series. The nerve is excited by tetanising shocks; the muscle is excited by tetanising shocks of its nerve; the retina is excited by exposure to candle-light.

The nerve record exhibits a series of undiminishing negative variations.

The muscle record exhibits a diminishing series of negative variations.

The eye record exhibits a slightly diminishing series of positive variations.

a series of retinal responses by electrical excitation.[1] It seems to me, however, that the comparison now made is a permissible one, the retina having presented to us a series of maximal effects by maximal stimulation by light. Such being the case, we may comment upon the remarkable endurance of the response, and express the opinion that such endurance is due not to insignificant chemical disintegration during activity, but to considerable and effective chemical reintegration during repose, and, it may be, during activity itself. I am of the opinion, on grounds that I hope shortly to make clear, that reintegration of retinal matter sensitive to light, goes on during its disintegration by light, as well as during darkness—that during activity retinal exhaustion is prevented by retinal invigoration. I shall return to this point presently.

(2) The fact that the retinal response is positive, whereas the responses of muscle and of nerve are negative (to the original upward current of rest of fig. 5), has not quite the simple significance that might at first sight be attributed to it. The actual direction of current of rest in the eyeball is unessential to the direction of the current of illumination; the former may be positive or negative, whereas the latter, which is the essentially interesting effect, is in general positive. It is advisable for any clear understanding to consider the latter without any reference to the former, and to realise its direction through the layers of the retina. If we consider an eyeball in its natural position, with cornea facing the sky and optic nerve stump to the ground, the direction of our current is upwards from the choroidal or pigment layer of the retina to its vitreous or nerve-fibre layer, and to be represented by an arrow pointing upwards from fundus to cornea—as we fancy we look at things—and thereafter through the galvanometer completing circuit from cornea to fundus. I usually take as my working mnemonic in the laboratory that the retinal response of an eye looking at the galvanometer "looks through" the latter. Where shall we look for the motive force driving our imaginary arrow? I think at the rod and cone layer of

[1] Note 8, p. 35.

the retina, where therefore you may picture as placed the tail of the arrow, the part to which the tense bowstring of photo-excitable stuff is applied and liberated by the stimulus of light. But let me repeat that we are to conceive that two simultaneous and opposite movements are promoted in the retina by light—the winding-up process by which potential energy is stored, the running-down process by which active energy is liberated.

I alluded to the grounds on which this view is based; let me now briefly expose these grounds.

The positive electrical effect of retinal illumination is assuredly not a single simple phenomenon, but a compound effect—the resultant of simultaneous and antagonistic forces. Being antagonistic, such forces must be conceived as two in number, or at least in two opposite camps if the components ultimately discovered should prove to be more than two. But however numerous such components might prove to be, they could not take effect otherwise than in one or other of two directions, which we shall therefore distinguish as positive and negative.

The signs by which we may recognise that the positive electrical effect of retinal illumination is double, are apparent at the commencement and at the end of prolonged illumination—at "make" and at "break" of light.

The main or principal effect *during* illumination is positive, and this positive effect gradually subsides during obscurity. Usually the initial effect at the commencement of illumination, *i.e.*, at *make* of light, is positive, but occasionally it is distinctly negative, and sometimes it is doubtful to an observer whether the very first motion of the galvanometer spot is negative or positive; sometimes again it is distinctly positive, then negative, before passing into the enduring positive position it takes up during illumination.

At the end of illumination the subsidence of the positive deflection is always preceded by a more or less well-marked sharp positive augmentation, *i.e.*, at *break* of light there is a sharp augmentation of the positive deflection during light, followed by gradual subsidence to the obscurity level.

One's first thought in presence of this somewhat puzzling break effect, is that the main positive effect during illumination may be a sign of pigment activity, while the terminal positive effect at break of light may be due to a movement of the cones. But on this view it is difficult to account for the fact that the terminal effect, if due to relaxation of cones, has not always its distinct initial counterpart at make of light by reason of a contraction of cones. I therefore hesitate to offer this in explanation of the facts, and shall content myself with the demonstration of the presence of two simultaneous and opposite effects,

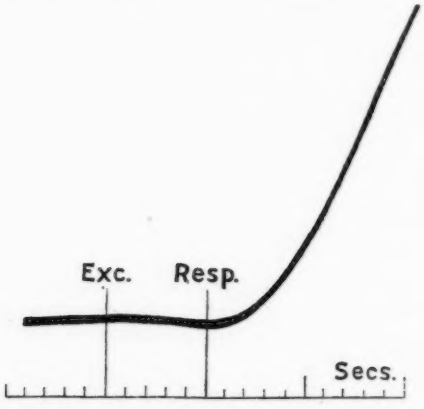


FIG. 9.

Eyeball of the second stage with a "period of hesitation" lasting five seconds.

without committing myself to an assertion that such opposite effects have their seat in the same or in different retinal elements.

The lost time of these make and break effects, more especially of the former, *i.e.*, the time elapsing between the commencement of illumination and the commencement of deflection, is highly significant of the double nature of the chemical change of which the electrical change is the outward and visible sign.

As regards the make effect in particular, or rather the

practically simultaneous make-break effect of a flash light, the interval between stimulus and deflection is physiologically enormous, obvious to simple observation as quite a long pause, and not requiring therefore a very rapidly travelling plate for its photographic registration.

We evidently have to do, not with a simple period of latency—such physiological inertia in the case of the retina is simply incredible—but with what I shall characterise as a period of hesitation, during which a tug-of-war, so to say,

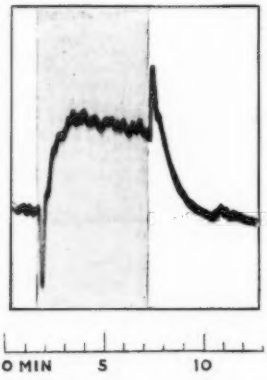


FIG. 10.

An old record of the retinal response to light (June 4, 1895; Candle at 2 feet = 25 units), which, although not of the usual type, I then regarded as being normal. In a sense it is so, but only for an eyeball in the second stage, as described in the text.

is taking place in the retina between two opposite forces or processes, positive and negative, that for a period counterbalance each other in the circuit.

A similar if less pronounced opposition of forces occurs at the end of illumination, when the two forces cease to act. But whereas we must suppose that at make of light, both forces commence to be evolved at almost equal rates, and that during light the positive force is the stronger, we must admit that at break of light, negative ceases more

suddenly than positive, so that a short positive *plus* precedes the more gradual positive *minus*. And if from any cause there should have been during the period of hesitation at make of light a sufficiently marked superiority of negative over positive, then we shall witness at make of light a distinct negative effect preliminary to the main positive effect—as shown in fig. 10.

The record, which was taken in July, 1895, was obtained on an eyeball in the second or transitional state, and Professor Kühne, when I showed it to him, recognised at once that it was the response of a partially-injured eyeball. The hint was not lost upon me. On returning to the subject last year I paid particular attention to the transitional types that are observed. And since I have mentioned Kühne's name in this connection to acknowledge a valuable hint, I should like to take the opportunity of showing you how closely some of my photographic records of 1899 reproduce the plotted curves of Kühne and Steiner of 1881. I have confronted in the two halves of fig. 11 Kühne and Steiner's fig. 1, which they give as representing the usual course of events in the isolated retina, and one of my own records of a response of an eyeball in the second stage. The similarity is sufficiently obvious.

That this is a reasonably probable view to take of the case is confirmed by the alterations of effect taking place in an eyeball accidentally mishandled, or left to become partially dry upon the leading off electrodes. From the freshly-prepared state, with an eyeball at its best, to the moribund state with an eyeball at its worst, I distinguish three stages.

In Stage I. the deflection at make of light is at once positive, the deflection during illumination is positive and increasing or stable; the deflection at break of light is positive and small, followed by gradual decrease of the main positive deflection to the normal obscurity level.

With lapse of time the main positive effect is less and less sustained during illumination, and the terminal deflection at break is relatively large. The deflection at make of light becomes "hesitant," being sometimes frankly

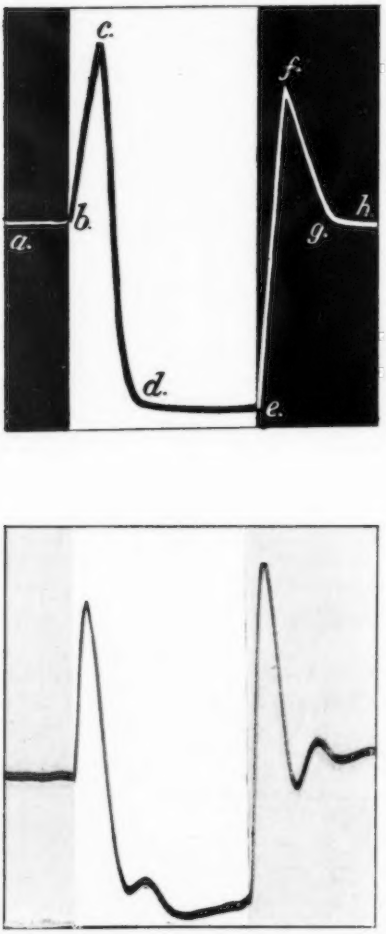
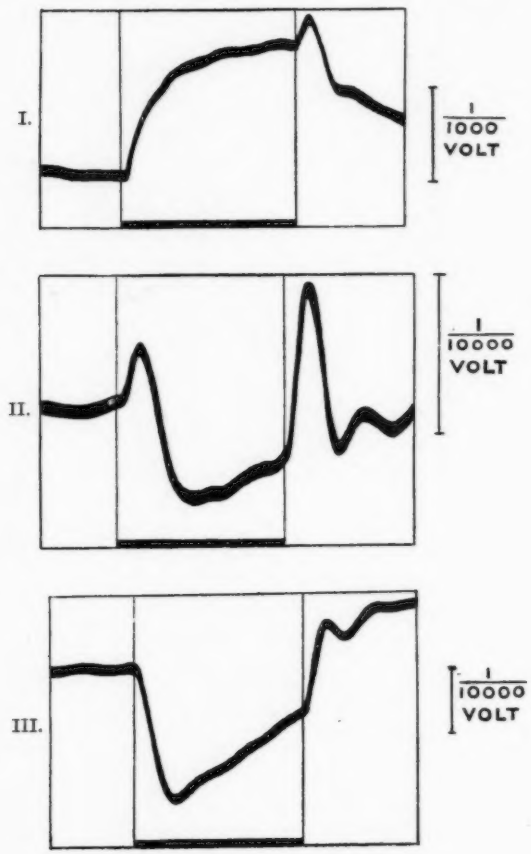


FIG. 11.

Comparison between Fig. 1 of Kühne and Steiner's second paper on retinal currents (1881) and a record of retinal response of the second stage, as described in the text.



FIGS. 12, 13, AND 14.

Electrical responses to illumination of the retina in the three stages described in the text.

(I.) Fresh eyeball. Considerable and augmenting positive effect. Small terminal positive increment.

(II.) Eyeball about six hours after excision. Initial positive effect followed by prolonged negative effect. Large terminal positive deflection.

(III.) Eyeball about twenty-four hours after excision. Clear negative effect during illumination.

In each case stimulation is made by exposure lasting one minute to a standard candle 2 feet from the eyeball.

(Fig. 8 is the continuation of Fig. 12, recorded from the same eyeball on a more slowly travelling plate.)

negative, sometimes positive with negative interruption, sometimes positive after a long period of hesitation.

In Stage II. the main positive deflection has disappeared, the state during illumination being neutral or actually negative. At make of light the deflection is positive, and markedly "hesitant." The terminal deflection at break of light is positive and large, being, in fact, the most prominent feature of the sequence.

In Stage III. the deflection is negative throughout illumination; at make the deflection is frankly negative, during light it is decreasingly negative; at break the deflection is positive, and the spot returns to its normal level of obscurity.

An even cursory review of these three stages, taken in conjunction with the peculiar period of hesitation at make of light, must reinforce the view that we are in presence of a double process, and that the dominantly positive effect of Stage I. has latent in it the opposite negative effect that is wholly unmasked in Stage III.

I have sought in many ways to separately influence the positive and negative effects—by drugs, by strong electrical currents, by raised temperature, by increased eyeball tension—acting on the supposition that by partial injury I might be able to, so to speak, wipe out the presumably more delicate process of constitution, and thus unmask the more enduring process of destitution. I find that the best and almost unfailing means of doing this is to partially injure the retina by compression of the eyeball. For an effective lecture demonstration, a fresh eyeball, giving the regular positive effect on illumination, may be taken off the electrodes, moderately compressed and rolled between the fingers, and replaced upon the electrodes; the effect of illumination on this massaged eyeball will almost certainly be negative.

Colour antagonism?

One may hardly be expected to make even the most cursory survey of positive and negative retinal changes without allusion to the comparative effects of the several

colours that make up white light—with reference of course to the well-known antagonism theory of Hering, white *v.* black, red *v.* green, yellow *v.* blue, which has played such a prominent part in the literature of colour-vision. We have seen that there is a very clear antithesis as regards the retinal effects of light and darkness, so that we might perhaps say that white and black are antagonists, and that white provokes an action while black promotes an opposed reaction. Can any similar antithesis be recognised between the two "dissimilative" colours red and yellow and the two "assimilative" colours green and blue, which, on the antagonism theory, are regarded as promoting opposite chemical changes in the retina?

On trial of this point we find in all cases that different colours give rise to electrical effects in one direction, though of varying magnitude. The order of efficacy in my own trials, made with carefully selected coloured glasses, has been:—red, blue, green, yellow, white, *i.e.*, in a sense that is obviously governed by luminosity. To quote an instance, the deflections were

With	Red	+ 4
	Blue	+ 9
	Green	+ 12
	Yellow	+ 16
	White	+ 33

Stimulation at 25 units. Illumination for 6 seconds at 1 minute intervals.

But we at once object that a possible opposition between the purely chromatic constituents has, perhaps, been masked by the white-valency common to all the colours, or by white light passing through the imperfect colour filters.

We therefore make two further series of trials (1) to learn whether the joint effect of two opposed colours is greater or smaller than their separate effects; and (2) to learn whether the separate effects of any two opposed colours are equally or unequally altered when the retina has been submitted to prolonged modification by one of the two colours.

I find (1) that taking two very weak colour stimuli, *e.g.*, red and green, the conjoint effect of both stimuli is always

greater than either of the separate effects, and not far short of their sum; (2) that a retina subsequent *e.g.*, to prolonged green stimulation or to prolonged red stimulation, exhibits equal fatigue to green and to red stimuli.

Here are two representative experiments—

I.

Red alone	+ 5
Green alone	+ 10
Red + Green	+ 14
White	+ 40

Stimulation at $\frac{1}{4}$ unit.

II.

Red	+ 21
Green	+ 28

Ten minutes' exposure to Green.

Red	+ 16
Green	+ 24

Ten minutes' exposure to Green.

Green	+ 22
Red	+ 15

Ten minutes' exposure to Red.

Green	+ 20
Red	+ 12

Ten minutes' exposure to Red.

Red	+ 8
Green	+ 18

Stimulation at 100 units. Lasting 10 seconds.

But for my own part, I must confess that I do not attach much value to these colour experiments. They are made upon the frog's retina; we have no reason to think that the frog is at all a judge of colour; the results show at most that the hypothetical chemical antagonism of colours is certainly not any deep-seated physiological antithesis pertaining to all retinal matter "excitable" by light. The psychologist remains as free as ever to believe or not to believe that the perception of colour by the human brain is three dimensional, and depends upon disintegration-cum-reintegration of a white-black substance, and of a red-green substance, and of a yellow-blue substance. But this to my

mind is a psychological chemistry, and I do not wish to wander too far afield from a physiological base.

Let me bring this chapter to a close by referring briefly to the positive and negative electrical effects that are manifested by ordinary nerve. The three stages just described as regards retinal effects, and the very probable double character of such effects, recall to mind the somewhat similar series of effects in freshly isolated dying nerve. Only whereas the three stages that I described in the case of nerve refer to electrical effects of electrical excitation, the retinal series refer to electrical effects of luminous stimulation.

The electrical response of isolated nerve tetanised by alternating currents is with lapse of time:—(1) a simple negative effect; (2) a negative effect immediately followed by a positive after effect; (3) a positive effect. Nerve in the second stage seems to be most clearly suggestive of the operation behind the scene of two opposite processes of action and reaction, of which the prominent manifestations in this case are successive. It would appear, moreover, that there is some kind of analogy between the early positive and late negative effects in retina on the one hand, and the early negative and late positive effects in nerve on the other hand, but I should be very unwilling to speculate very far along this superficial and obvious analogy. We may, however, consent to speculate in moderation, and admit that just as in the retina there is a store of matter that is formed, and that is consumed under the excitation by light, so in nerve there is analogous stored matter formed by activity and subserving activity.

Significance of the Medullary Sheath. Fatigue of Non-Medullated Nerve.

Naked gray matter, as of a nerve centre, is very rapidly exhausted, and has to be replenished at leisure from the nutritive fluids. Protected gray matter, as the conductile axis of medullated nerve-fibre, is extraordinarily inexhaustible because its wear and tear of action is instantly effaced

by the restorative reaction of its white envelope; just as the highly mobile elements of the retinal organ, provoked to action and therefore to expense by light, are *pari passu* kept supplied and protected from exhaustion out of the store of pigment that is our visual inogen.

It is by action and reaction between core and sheath that the nerve-impulse is propagated along a medullated nerve-fibre. It is by the same action that the impulse is insulated within a definite conducting fibre. And by the same means there is secured to the essential part—the grey core—an almost instantaneous restoration of expended matter necessary to unimpaired function rapidly repeated.

Do we ask for evidence of a commerce of matter between the grey core and its white jacket of phosphorised fat? We have such evidence—and of the most cogent—in the first gross fact of Wallerian degeneration. The grey core of a nerve-fibre is the arm of a nerve-cell which is its body, and when the nerve is cut the arm degenerates away from the body. The first and most obvious change of structure takes place, not in the core itself, which was in continuity with the cell body, but in the discontinuous sheath, by which it is enveloped and nourished. The disordered nutrition of the principal part—the axis, is first visibly manifested by the superadded and subordinate part—the sheath.

If this hypothesis be well founded, we should expect that non-medullated nerve, examined as to exhaustibility, would be found to conform to the type of exhaustible muscle rather than to the type of inexhaustible nerve.

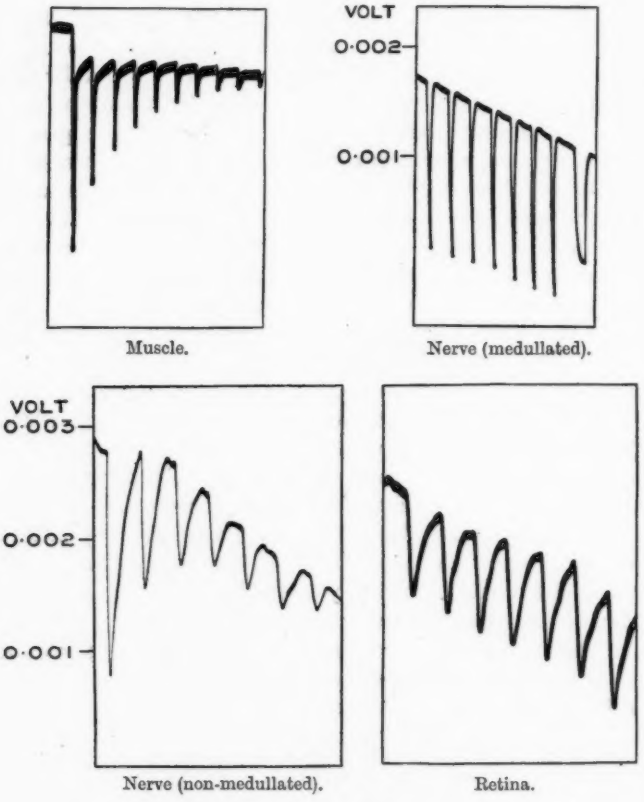
Miss Sowton, who at my request has investigated the point upon the olfactory nerve of the pike, has as a matter of fact found this to be the case.

Veratrine and Protoveratrine.

Veratrine, $C_{32}H_{49}NO_9$, and protoveratrine, $C_{32}H_{51}NO_{11}$, are two closely related alkaloids derived from green and from white hellebore respectively. The former, as is well known, has a specific action upon muscle, and causes its contraction to be extraordinarily prolonged. A veratrinised

muscle contracts vigorously but does not relax. Pure veratrine has comparatively speaking no action upon nerve.

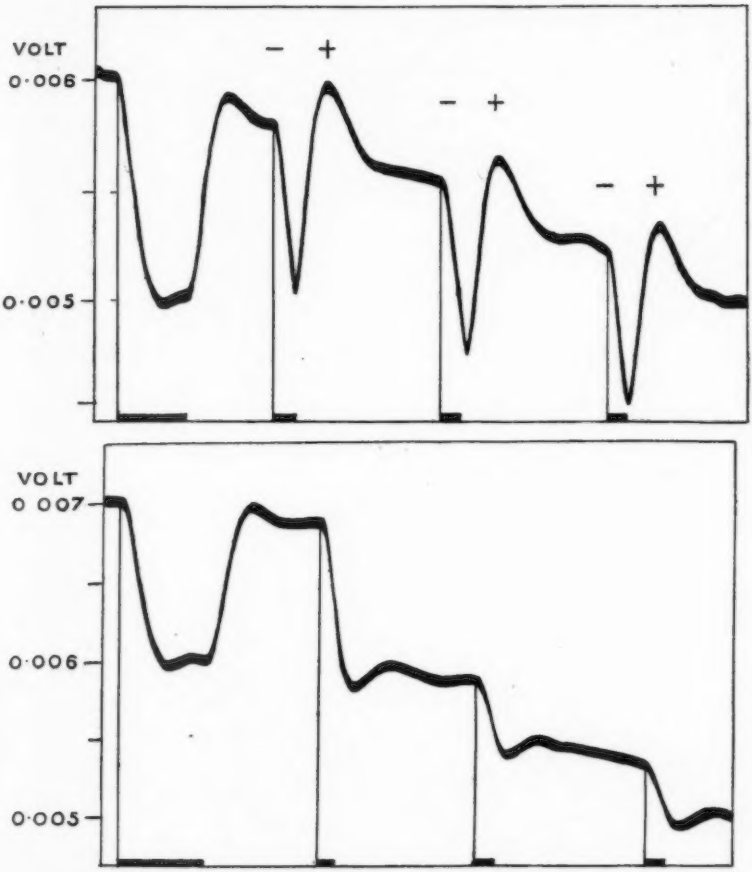
Protoveratrine, which has recently been identified and distinguished from veratrine by Boehm, has a specific



FIGS. 15, 16, 17 AND 18.

Portions of records of ordinary muscle, of medullated nerve, and of non-medullated nerve (olfactory nerve of pike) similarly excited—to show that non-medullated nerve resembles muscle and differs from medullated nerve, as regards the manifestation of fatigue.

Fig. 18 is a similar retinal series of responses to light, exhibiting little or no sign of fatigue (retina of the third stage).



FIGS. 19 AND 20.

To illustrate the contrast between veratrine and protoveratrine.

In each case a frog has received an injection of one drop of a $\frac{1}{2}$ per 100 solution of the alkaloid (=about 0·0005 gramme, *i.e.*, a very large dose). Between $\frac{1}{2}$ and one hour later the apparently dead frogs have been pithed and a sciatic nerve of each has been removed and placed upon the electrodes.

In each case three electrical responses (at intervals of one minute to tetanisation lasting for six seconds) have been recorded.

The three veratrine responses are normal and undiminishing; each response exhibits a negative effect during excitation and a positive effect after excitation.

The three protoveratrine responses are sustained and diminishing; each response exhibits a negative effect during and after excitation.

The deflection to the left of each record is a standard deflection made by passing current from $\frac{1}{1000}$ volt through nerve and galvanometer. It serves to give the voltage scale of the nerve-responses, and shows to what extent the galvanometer is "dead-beat."

action upon nerve, and comparatively speaking no action upon muscle. It causes the negative variation of excited nerve to be extraordinarily prolonged. The fact in itself is of considerable interest, inasmuch as it is at present a solitary and very clear case of two drugs, closely allied chemically, and having each a sharply defined predilection for muscle or for nerve. Veratrine acts upon muscle. Protoveratrine acts upon nerve. And the action of protoveratrine upon nerve is very similar to the action of veratrine upon muscle. Just as in muscle veratrine impedes the relaxation of a contracted state, so in nerve protoveratrine impedes the positive reaction that is normally associated with, or consequent upon, excited activity. Normal nerve gives during excitation a negative variation that signifies disintegrative change, and after excitation a positive return to, or it may be beyond, the normal level of a quiescent state, signifying reintegration. Veratrinised nerve acts and reacts normally. Protoveratrinised nerve exhibits a well-marked negative sign of action during excitation, but little or no positive sign of reaction after excitation. And in correspondence with this failure of positive reaction, the succession of action-effects exhibits rapidly progressing exhaustion. A succession of negative variations of normal (or of veratrinised) nerve, exhibits from first to last little or no diminution. Successive negative effects on protoveratrinised nerve are permanent and rapidly diminishing. Exhaustion is apparent in medullated nerve when its positive process of restitution is impeded.

III.—The Law of Reaction.

The simplest problem that we may set ourselves to resolve in the case of any excitable tissue—such as muscle, nerve or retina—is to determine how much responsive effect follows upon how much exciting cause.

And we shall most conveniently summarise our results by plotting a curve, marking off magnitudes of cause (= excitation) along the X axis and magnitudes of effect

along the corresponding ordinates parallel with the Y axis.

Taking, for example, a series of stimuli of arithmetically increasing magnitudes, 1, 2, 3, 4, 5, and having determined that the corresponding effects come out at the magnitudes 34, 58, 72, 82, 90, the cause-effect curve plotted out on this principle would be thus:

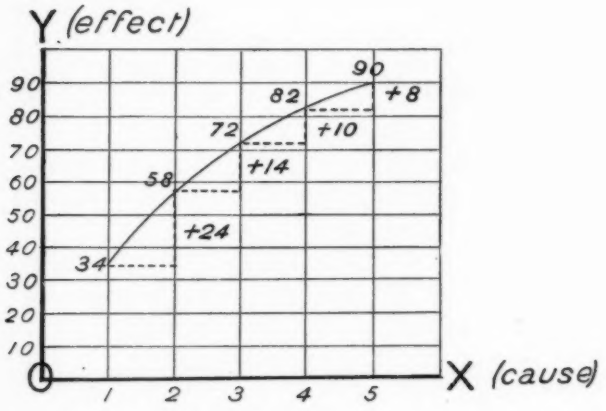


FIG. 21.

Curve exhibiting the electrical response (Y) of the retina to luminous stimulation (X) of arithmetically increasing magnitude (energy). The unit of light in this case is $\frac{1}{100}$th part of the light of a standard candle at a distance of 1 foot, *i.e.*, the light of a standard candle at a distance of 10 feet.

viz., concave to the abscissa OX, and exhibiting at a glance that + 24 + 14 + 10 + 8, diminishing increments of effect, are caused by equal increments of excitation.

Now let us plot out the results of an actual experiment in which the cause was luminous stimulation, and the effect an electrical response of the retina.

The X series was 1, 2, 4, 6, 8 units.

The Y series was 44, 60, 68, 72, 75 degrees of scale.

The plotted curve is obviously concave towards the abscissa OX, *i.e.*, equal increments of luminous excitation cause diminishing increments of retinal change.

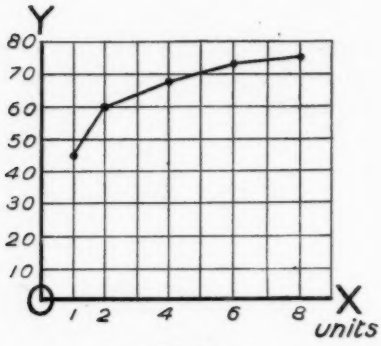


FIG. 22.

Curve exhibiting the electrical response (Y) of the retina to electrical stimulation (X) of arithmetically increasing electrical energy (condenser discharges).

Let us take as another illustrative instance an experiment in which the cause was electrical stimulation and the effect a subsequent electrical response of the retina.

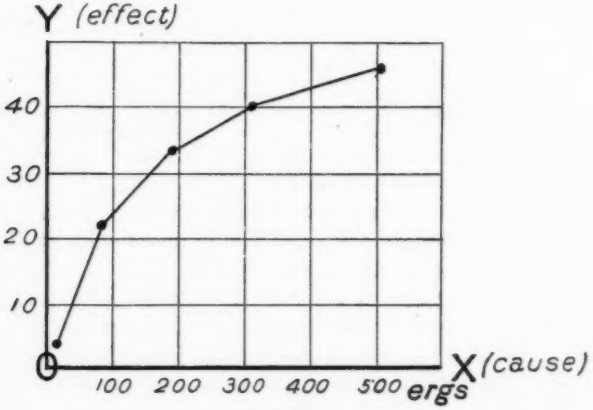


FIG. 23.

The X series was 20, 80, 180, 320 and 500 ergs.
The Y series was 4, 22, 34, 40 and 45 degrees of scale.

As before, the cause-effect curve is concave to the abscissa OX, *i.e.*, equal increments of cause produce diminishing increments of effect.

The cause-effect curve of stimulation and sensation, as expressed by the logarithmic law, is of a precisely similar type, *i.e.*, equal increments of sensation require increasing increments of stimulation, or otherwise expressed, diminishing increments of sensation are produced by equal increments of stimulation. Taking, *e.g.*, intensity of light along the X axis, and intensity of sensation along the Y axis, we require geometric increase of X to produce arithmetic increase of Y, or otherwise expressed, arithmetic increase of X produces logarithmic increase of Y.

This well-known and much criticised law of sensation, which with reservation may be admitted to be the fundamental law of psychophysics, holds good only within certain limits of moderate stimulation. Within the moderate range of ordinary daily sensation, it is obviously reasonable that equal increments of stimulation should effect decreasing increments of sensation, and that all sensation should find its limit with maximal alteration of nerve-matter. Between objective stimulus and subjective consciousness we have to consider physiological change of nerve-matter, of which change of consciousness is the symptom. An external stimulus *X* arouses physiological change of nerve-matter *Y*, which material change or internal stimulus *Y* is the basis of the sensation *Z*. Firstly, external stimulus, secondly, physiological change, thirdly, sensation—a relation between first and third such that equal increments of the former arouse decreasing increments of the latter. Is this limitation of effect, which is so clearly pictured in the concave curve, a limitation of physiological change *Y* producible by stimulation *X*, or a limitation of psychical change *Z* producible by physiological stimulation Y? Clearly, I think, the former—since we find in the case of the retina, or indeed in any case where the physiological effects of excitation are experimentally accessible, that equal increments of excitation arouse diminishing increments of physiological effect.

Less clearly, and with less confidence, yet, I think, with some degree of justification, we may assume, at least for the sake of clear thinking, the corollary to this conclusion, viz., that there is no disproportion between the physiological change *Y* and the psychical sensation *Z*, *i.e.*, that equal increments of sensation belong to equal increments of physiological change; or, again, that the symptom felt is the true arithmetic measure of the physiological state of nerve-matter which is its basis.

Let us consider rather more closely the two extremes of minimal and maximal sensation.

With indefinite increase of stimulation it is clear that we cannot have indefinite increase of physiological change, nor, therefore, indefinite increase of sensation. There must be a maximal effect. All change in living matter is, indeed, self-limitative; the activity of all living matter expends itself, and is arrested by the products of activity; with excessive stimulation the curve of sensation ceases to rise and then falls away from its maximum, losing itself finally in some other kind of sensation, or in actual anæsthesia through mere physiological exhaustion of nerve matter. Does such blunting of sensation come to pass through the agency of waste-products of excessive activity, of which carbonic acid is the representative? We may imagine so, but we may hardly say so.

At the lower end of the scale, down near the threshold of sensation, it is hardly reasonable to expect that a concave curve, constructed on the same formula as that, expressing the relation between moderate stimulation and moderate sensation, should express the relation between minimal stimulation and minimal sensation. Such a curve, steepest at its commencement, *i.e.*, with greatest increments of Y for given equal increments of X, would signify that close to the threshold absolute differences of X of infinitesimal magnitude take effect upon consciousness, *i.e.*, a condition of extraordinary hyperæsthesia towards the minutest stimuli of our environment.

We should expect to find, and in point of fact we do

find by careful experiment, that the minimum perceptible difference, *e.g.*, of light, is a considerably higher fraction at low intensity than at moderate intensity, *e.g.*, 1 in 5, or 1 in 10 at low intensity, as compared with 1 in 50 or 1 in 100 at moderate intensity. We all know indeed that it becomes more and more difficult to see print distinctly with fading light. This signifies that we are relatively less sensitive to differences of weak light, relatively more sensitive to differences of moderately strong light—in other words, that the early rise of the curve from the threshold is by increasing increments of sensation, *i.e.*, convex to the abscissa. A curve beginning thus, convex to the abscissa, and subsequently becoming concave to the abscissa, may be briefly designated as an S-shaped or sigmoid curve. To say that the cause-effect curve (cause measured along the X axis, effect along the Y axis) is a sigmoid curve, is to say in brief that equal increments of cause from minimal to maximal produce at first increasing increments of effect, and subsequently decreasing increments of effect. Fig. 24 is intended to make this point clear.

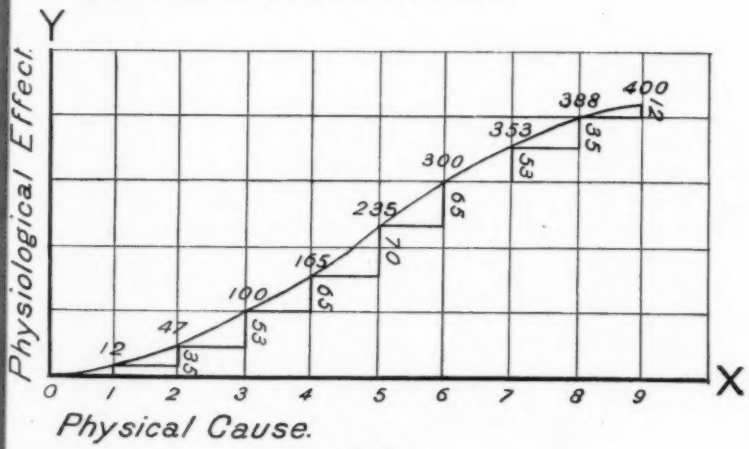


FIG. 24.

Curve exhibiting the electrical response (Y) of the retina to luminous stimulation (X) of low arithmetically increasing intensity (energy). The unit of light is here one quarter of the unit taken for Fig. 21, *i.e.*, the light of a standard candle at a distance of 20 feet.

I consider that a sigmoid curve as just defined gives graphic form, not merely to the relation between physical excitation and psychical sensation, but to the general relation between physical cause and physiological response in the excitation of living matter, of nervous matter, and in particular of the retinal substance excitable by light.

I look for, and find it, in the case of muscle, and in the case of nerve, and in the case of the retina, and venture to speak of it as the law of reaction.

A comparatively rough series of trials suffice to bring out data that are plotted in a curve concave to OX, *i.e.*, with diminishing increments of effect to equal increments of cause.

A more delicate series of trials, with stimuli of low intensity and increasing by smaller increments, is necessary to bring into evidence the initial convex portion which is comparatively short.

Fig. 25 is a good example of it upon the retina, strength of light being plotted along the X axis, magnitude of electrical response along the Y axis.

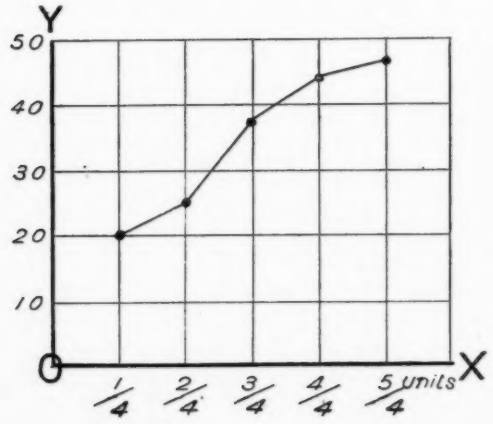


FIG. 25.

Let me try to illustrate the great general significance of a sigmoid curve, such as I have urged as symbolising more faithfully than the wholly logarithmic curve the law of physiological reaction, which I take to be inclusive of the law of psychical reaction.

The adequate performance of any human task is the effect of human energy—How much energy X to how much result Y in the asymptotic approach towards perfection?

In, let us say, the learning of a language, we know that the first steps cost much, and that the effect rises slowly; then the upward progress becomes more rapid, successive equal increments of energy give successive increasing increments of knowledge; finally progress slackens, the last steps towards perfection cost energy far in excess of those taken within the range of mediocrity.

The easiest part of any task, that in which the smallest effort seems to give greatest progress, is its middle portion; the two hardest and most expensive parts are its beginning and its end.

NOTES AND REFERENCES.

(1) Inexhaustibility of Nerve-Fibre (p. 5).

I have insisted upon this point upon more than one occasion —for the first time in 1885 and in 1886 in two successive reports to the Scientific Grants Committee of the British Medical Association (*B. M. J.*, July, 1885, and July, 1886), for the second time in 1891 in a paper on the "Sense of Effort," communicated to the Neurological Society (Brain, 1891, pp. 179-433), and for the third time in the Croonian Lecture for 1896 (*Phil. Trans. R. S.*, 1897).

Wedensky in 1883 (*Cbt. f. d. Med. Wissenschaft*) and Bowditch (*J. of Physiology*, 1885; *Du Bois-Reymond's Archiv.*, 1890), came to the same conclusion, viz., that nerve-fibre is practically inexhaustible, and expressed themselves far more unreservedly than I then did, or should care to do now. The negative variation of nerve is an ultimate sign of life, and even if electrotonic effects are excluded, is not a safe proportional indicator of the capacity for function which requires not merely a living state,

but a living state of high excellence. A nerve that can conduct nerve-impulses will certainly manifest a negative variation, but it does not follow that a nerve that will manifest a negative variation is capable of conducting nerve-impulses.

I share the opinion expressed by Pflüger to the effect that the negative variation is itself proof positive of a chemical change in active nerve, that activity if long enough and strong enough *must* cause chemical expenditure, and, therefore, fatigue. But the anomaly of apparent inexhaustibility of nerve in the presence of undeniable chemical change, is in my view reconciled when we have recognised the extraordinary rapidity with which exchange of matter is effected between gray axis and white sheath. I regard the white sheath as forming a store of nutrient matter surrounding the gray axis—feeding it and fed by it—enabling the function to be performed, and itself a secondary deposit aroused by the function. In short, I regard medullated nerve as supplying a striking case of "complementary nutrition"—of that "consensus partium" between two mutually interdependent tissues according to which waste matter of each tissue is raw material to the other tissue.

(2) Fatigue of the End-Plate (p. 5).

In the illustration given in the text the effect on muscle has been produced by excitation of its nerve, and the decline is, therefore, by progressive fatigue of the end-plate.

This point was established in my reports to the Scientific Grants Committee of the British Medical Association for 1885 and 1886 (*B. M. J.*, July, 1885, and July, 1886), when I compared the state produced by fatigue and by nerve-degeneration with that produced by curarisation, and formulated the conclusion that the motor end-plate is the weak link in the neuro-muscular chain, being the point at which the function of transmission is first affected with excess of action, or with disordered nutrition or with the onset of death, just as in curarisation.

In voluntary action—involving changes throughout the tract from Rolandic cell to periphery—the chiefly fatiguable points are presumably the cells or points denuded of white matter, viz., the cerebral cell, the spinal cell, and the motor end-plate. I have elsewhere formulated the law that fatigue effects declare themselves with diminishing gravity from centre to periphery, *i.e.*, that central fatigue is limitative of peripheral fatigue.

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(3) Isolated Nerve as a Test-Object (p. 5).

The general application of the electrical method to the pharmacodynamics of isolated nerve was first broached and described in a series of three papers communicated to the Neurological Society in 1896, and published in Brain, 1896, pp. 43, 277, and 569.

The particular case of carbon dioxide is considered at length in the Croonian Lecture for 1896 (*Phil. Trans. R. S.*, 1897).

Other developments of the same subject are contained in the Proceedings of the Royal Society and of the Physiological Society for the years 1895 to 1899.

The fundamental principles of the method are given in my "Lectures on Animal Electricity," 1897.

(4) The Axiom of General Physiology, p. 7.

The expression is of Claude Bernard (*Phénomènes de la Vie*, 1879, vol. ii.).

"On peut distinguer deux ordres de phénomènes :—

"(1) Les phénomènes de fonctionnement, ou encore d'usure, ou de *destruction vitale*.

"(2) Les phénomènes de formation, ou de création vitale, ou encore de *synthèse organique*. . . .

"Les deux types ne sont jamais isolés; ils sont indissolublement connexes, et la vie de quelque être que ce soit est caractérisée précisément par leur réunion et leur enchaînement; ils représentent les deux phases du travail vital.

"Cette vérité constitue, ainsi que nous l'avons dit ailleurs, *l'axiome de la physiologie générale*. On peut être assuré que toute doctrine qui serait directement ou indirectement en contradiction avec cette donnée fondamentale est fausse, et que le principe de l'erreur est précisément dans cette contradiction."

(5) Positive and Negative (pp. 8 & 9).

It is purely matter of convenience and convention which of two opposed movements we may choose to designate as positive and which as negative. But once having made our choice, the convention must be adhered to throughout the course of any given argument.

As regards muscle, the usual custom is to regard contraction as the positive act, relaxation as the negative act.

As regards the chemical changes, however, we are naturally led to take negative change (katabolism) as the chief feature of contraction, and to regard positive change (anabolism) as the reaction during relaxation.

As regards the electrical change, it is usual to refer to the poles of the external circuit, and not to the electro-motive elements. On this understanding the pole connected with active tissue is negative, just as the pole connected with the zinc of a voltaic couple is negative. In physiological literature active tissue is termed negative, whereas in physics the zinc carrying the negative pole is termed electro-positive.

I venture to think that the electro-motive action of active tissue is more vividly pictured when referred to an electro-positive element as the driving force, than when it is indicated by negative pole. Moreover, the latter custom introduces misleading expressions, such as "active tissue electro-negative to normal tissue," "negativity of action," &c.

Physiologically *active* tissue, in which presumably disintegrative exceeds reintegrative change, like the zinc of voltaic couple, is *electro-positive*, and its external pole is *negative*. Physiologically *quiescent* tissue, in which presumably reintegrative exceeds disintegrative change, is *electro-negative*, and its external pole is *positive*.

In any case, where there is danger of ambiguity from the terms positive and negative, direction of current should be clearly indicated by words or by diagram.

(6) Retinal Response to Light (p. 9).

The variation of current of the illuminated eye was discovered by Holmgren in 1871 (*Cbt. f. d. med. Wiss.*, 1871, p. 423), and further investigated in 1873 by Dewar and McKendrick (*Trans. R. S. Edin.*, 1873, p. 141; *Journ. of Anat. and Physiology*, vii., p. 275, 1873), and in 1880-81 by Kühne and Steiner (*Unters. a. d. physiol. Inst.*, Heidelberg, vols. iii. and iv., 1880-81).

Holmgren described the retinal response to light as being positive in the case of the frog, negative in the case of mammals.

Dewar and McKendrick sum up their observations on the frog's eye as follows:—"The natural electro-motive force is in the first place increased, then diminished; during the continuance of light it is still slowly diminished to a point where it remains tolerably constant; and on the removal of light there is

a sudden increase of the electro-motive power nearly up to its original position."

Kühne and Steiner in their second paper (*Sehorgan*, 1881) give an account of retinal phenomena in many respects similar to that which I have given in the text, of the successive changes as they came under my observation. K. and S. insist particularly upon the permanently positive response of the normal eyeball and upon its alterations by injury. They consider the negative effect to be produced by partial detachment of the retina, and the positive effect during illumination to be the expression of a regenerative influence of the retinal epithelium.

These and other points will be more fully discussed in a paper that I am now drawing up for communication to the Royal Society.

Quite recently (November, 1899), Beck has described the retinal response of the cephalopod retina as positive (*Pflüger's Archiv.*, vol. lxxviii., p. 129, 1899).

(7) Latency of the Retinal Response (p. 12).

Dewar and McKendrick made the first approximate measurements of latency, and found it to be not more than $\frac{1}{10}$th sec.

S. Fuchs (*Pflüger's Archiv.*, vol. lvi., p. 408, 1894), with the aid of Bernstein's rheotome, measured it as being 0·0004 to 0·006 sec.

(8) Tetanisation of the Retina (p. 8).

I have since made the experiment alluded to in the text. The results are altogether similar to those obtained by illumination. Alterations of retinal excitability are manifested in a nearly parallel sense to both kinds of stimulation. During and after tetanisation the retinal excitability to light is increased. The results of these experiments will be published shortly.

(9) Hering's Theory of Colour Vision (p. 18).

Hering first promulgated his celebrated theory in the sixth of a series of communications to the Vienna Academy of Sciences in the years 1872 to 1874, collected and reprinted for the second time in 1878 under the title *Zur Lehre vom Lichtsinne*.

The paraphrases of Hering's theory current in English text-books are far less subtle and indefinite than the version of

Hering himself, who writes as follows in the introduction of a paper by Hillebrand (*Wiener Sitzungsberichte*, February, 1889, p. 73) :—

"The psycho-physical vision-stuff may accordingly be regarded as a mixture of three qualitatively different substances. Nevertheless, I signified long ago (*Zur Lehre vom Lichtsinne*, § 42) that I gave this form to the theory only for the sake of greater distinctness, and that I consider it to be fundamentally more correct to say that the psycho-physical vision-stuff is capable of qualitatively different kinds of Dissimilation and Assimilation, and that each of these innumerably different kinds of D. and A., assuming three principal kinds of D. and A., can be conceived as broken up into three components, each of which corresponds to one of these three principal kinds of D. and A. It is, no doubt, more intelligible to most people to say that each visual sensation may be conceived as composed of given primary or elementary sensations, in given proportions, than to say that each visual sensation takes, in the pre-arranged three-dimensional variability of visual sensation, a given place in relation to three given sensation series; and it is more intelligible to regard the vision-stuff as a mixture of three separate substances, each of which can be altered in two qualitatively opposite senses (D. > A. and A. > D.), than to say that the variability of state of vision-stuff is three-dimensional."

Helmholtz's theory, with which Hering's is generally quoted as being in flagrant opposition, is hardly more accurately reproduced in English text-books. In the second edition of his "Physiological Optics" (1889, p. 349), he assumes the hypothetical existence not merely of three sorts of retinal elements, but of three kinds of photo-chemically changeable substances, and of three kinds of cells in the cerebral cortex.

On a hypothesis of antagonistic colours of so meta-chemical a character as Hering's, positive results of experiments of the character described in the text might hardly be expected.

Previous experiments of the kind have been published by Dewar and McKendrick, who observed a different order of efficacy to that given in the text, viz :—red = 10, yellow = 10, green = 8, and blue = 4. Subsequently, however, they give the relative efficacy of colours as being governed by luminosity.

R. Dubois (*La Pholade Dactyle*, Paris, 1892) tested the efficacy of different colours upon the mechanical response of the integuments of *Pholas dactylus* with the following result :—red = 3, yellow = 13, green = 10, blue = 8. These numbers represent amplitude of reflex contraction of an integument excited by

spectral colours. With coloured glasses the results were:—red = 3, yellow = 13, green = 10, blue = 8. With the same set of glasses—which Professor Dubois was good enough to send to me—I obtain electro-motive responses of the frog's retina as quoted in the text, viz.:—red = 4, yellow = 16, green = 12, blue = 8.

The researches of Dubois on the integument of *Pholas* are of great interest as regards the general physiology of luminous excitation, but are not yet sufficiently appreciated. There is a close structural and functional analogy between the retina and the integument of *Pholas*. Both respond to light—the former by an act of vision and by an electro-motive change, the latter by a reflex mechanical movement and an electro-motive change. The physiological histology of the sensitive surface is as follows:—An external layer of pigment-cells is connected with a superficial layer of muscular fibres that contract in response to luminous stimuli; this initial direct contraction mechanically stimulates subjacent nerve-cells, and is followed, after a short interval of time, by a reflex contraction of the entire longitudinal musculature of the syphon. Histologically, the dermic element excitable by light is composed of (1) a pigment-cell, (2) a contractile fibre, and (3) a nerve-cell. Physiologically, the stimulus of light arouses a dermic phosphene, of the nature of a tactile phenomenon, *i.e.*, light provokes chemical change in a pigment-cell, which in turn provokes movement of a contractile fibre, which in its turn mechanically excites a nerve-cell. This series of events at the periphery constitutes the physiological stimulus of which a reflex contraction of the syphon is the final consequence, just as a reflex movement of self-defence or flight is the final consequence of the retinal changes aroused by retinal images higher in the animal scale.

(10) Hering's Positive After-Effect (p. 20).

A full description was first given of the after-effect of nerve-excitation and of its possible significance by Hering in 1884 (*Wiener Sitzungsberichte*, 1884, p. 137). The point was further investigated in Hering's laboratory by Head (*Pflüger's Archiv.*, vol. xl., p. 207, 1887).

(11) Three Stages of Nerve-Response (p. 20).

The three stages into which I found it necessary to distinguish the response of isolated nerve, and the possible signifi-

cance of the phenomena observed in each stage, are fully discussed in the Croonian Lecture for 1896 (*Phil. Trans. R.S.*, 1897, pp. 23 and 62).

(12) Rapidity of Nerve-Polarisation (p. 20).

Hermann pointed out in 1888 (*Pflüger's Archiv.*, vol. xlii., p. 1, 1888) that nerve, unlike muscle, exhibits no difference of resistance, whether the test-current be a constant or an induced current. Nerve is eminently polarisable (Herman's well-known theory of electrotonus rests upon this basis), but its polarisation and depolarisation take place with such extreme rapidity that the polarisation counter-current has time to develop even during the passage of an induction current.

Following up this point I found that the apparent resistance of normal nerve is higher to the comparatively "long" induced current at make than to the comparatively "short" induced current at break. Also that the apparent resistance of nerve to any current is diminished by diminution of polarisation counter-current, when the nerve-matter has been "immobilised" by chloroform (*Proc. Physiol. Soc.*, November, 1898).

(13) Veratrine and Protoveratrine (p. 21).

The action of *veratrine* upon muscle was first described in 1862 by Harless (*Ztschr. f. rat. Med.*, iv., p. 97, 1862), and further studied by v. Bezold and Hirt (*Unters. a. d. physiol. Lab.*, Würzburg, 1867), J. L. Prevost (*Gazette médicale de Paris*, 1867), Fick and Boehm (*Arb. a. d. physiol. Lab.*, Würzburg, 1873), and many others.

Protoveratrine was identified and separated in 1890 by Salzberger, and its properties investigated by Watts Eden in the Pharmacological Institute of Leipsig, under the direction of Professor Boehm. W. Eden observed that protoveratrine, although poisonous to muscle, does not cause the prolongation of contraction characteristic of veratrine. The protoveratrine with which I made the experiments alluded to in the text, was kindly given to me for the purpose by Professor Boehm. I have described the results somewhat more fully in the jubilee volume of the *Société de Biologie*, Paris, 1899, p. 347.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

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INTRODUCTION.

MUCH as we feel the need of some other name under which to describe the affection, seven cases of which we are about to record, most of the papers that have appeared on the subject have borne the above or some similar title, so that to introduce a new name for the affection now would probably lead to confusion, however much it might serve to obtain for our own cases recognition that they are examples of a distinct morbid entity.

By combined degeneration of the spinal cord is meant an affection in which tracts of different function are concomitantly affected. It is, therefore, obvious that under such a title might legitimately be included a variety of different affections, each of which is characterised by the concomitant implication of tracts of different function. Examples of such affections are to be found in the "Ataxic Paraplegia" of Gowers, if there be such an affection distinct from the class of case with which we are more immediately concerned in our present paper; "Friedreich's Ataxy," "Cerebellar Heredo-Ataxy," such cases of "General

Paralysis of the Insane" as present degeneration in the posterior columns of the cord in conjunction with similar change in the lateral columns, and the like.

It therefore follows that there is need for a name that would serve to distinguish the class of case we are about to describe, from the affections that have just been enumerated, for it possesses a very definite clinical picture, not as a rule difficult of recognition, and a morbid anatomy which is as characteristic as that of tabes or any other disease of the spinal cord, with as distinctive a morbid picture as that possessed by the disease just mentioned. A name other than "Combined Degeneration," would undoubtedly do much to establish the affection as a separate and distinct morbid entity, would facilitate its study, and free it from the entanglements by which it is at present hampered, in consequence of the fact that so many different diseases of the spinal cord are characterised by combined degeneration of tracts of different function. We however, feel, that at present we shall probably be serving a more useful purpose by retaining the term "Combined Degeneration," and must trust to the "Subacute" as being sufficient to exclude most other forms of combined degenerations of the spinal cord, such as are likely to be confused with the affection now under consideration.

Its present name is, however, not the only entanglement from which it would be well to free the malady. The cases that were first recorded, and which led to the recognition of this disease as a distinct morbid entity, were described by Lichtheim as instances of cord changes associated with anæmia. Leichtenstern, the records of whose cases were next to appear, described the affection as "Progressive pernicious Anæmia in Tabetic Patients." In this way it has come about that the affection has become intimately bound up with anæmia, which has been variously described as "profound," "pernicious," "grave," "fatal," and so on. As a consequence of this, two totally distinct conditions have been confused, and in the literature that has grown up around the publications of Lichtheim and Leichtenstern we find cases of each recorded in a manner that suggests that

the authors regard the affections as belonging to the same category, or, indeed, as if they are identical. Anæmia, in its relation to the subacute combined degeneration of the spinal cord, has to be considered from three points of view, in so far as the publications on the subject are concerned. There are the cases of subacute combined degeneration of the spinal cord with which we have to deal more directly in this paper, in some of which cases anæmia is a feature in the symptomatology; secondly, cases of anæmia in which certain symptoms arise which point to some disturbance of nerve function and in which certain changes are found in the spinal cord after death; and, lastly, cases of severe anæmia in which there have been no clinical phenomena pointing to disturbance of nerve function, but in which, nevertheless, histological examinations have revealed certain definite morbid changes in the spinal cord.

Cases of the first group are readily recognised clinically in consequence of the very definite symptomatology which they present, the phenomena pointing to serious structural defects in the nervous system; and the morbid changes found on necropsy serve to distinguish them from any other affection of the nervous system. In some of the cases anæmia is a striking feature in the symptomatology, while in others, if present at all, it is slight and unobtrusive.

The second class comprises a group of cases in which vague symptoms of a more or less indefinite character arise in the course of severe anæmia, which may or may not be characterised by the features which are supposed to be diagnostic of the so-called pernicious variety. The majority of the symptoms indicating implication of the nervous system point to interference of function consequent on molecular changes in the nerve elements rather than to gross structural changes in these parts. Histological examination, nevertheless, reveals gross changes in some such cases, and while these cannot be said to be identical with the changes found in the subacute combined degenerations, there is sufficient to make it impossible to deny that the changes found in these cases may represent an earlier stage of the affection which, when fully developed, presents so

characteristic a morbid picture as that which we propose to lay before our readers.

The third group is composed of cases in which, though structural changes are found in the spinal cord on necropsy, there have been no symptoms during life which have pointed to affection of the nervous system. Nonne, Minnich, Burr and others have devoted attention to such cases, and all that can be said in this connection is that although they prove that structural changes may occur in the spinal cord in cases of anæmia, they do not admit of the interpretation that these defects are the earliest changes the full development of which are seen in the subacute combined degenerations, on examples of which our present paper is based.

All the cases like our own that have been published from the National Hospital for the Paralysed and Epileptic belong to the first category, and in all of them there has been the characteristic clinical picture supported by the equally typical morbid appearances found after death.

The first paper from this source was by the late Dr. Bowman and dealt with a single case ; a paper by Dr. James Taylor dealt with two cases, and one by one of us (J. S. R. R.) was based on three such cases.

We are indebted to Dr. Hughlings Jackson, Dr. Buzzard, Dr. Bastian, Sir William Gowers and Dr. Ferrier for permission to publish the following cases, which were under their care in the National Hospital, and we take this opportunity of thanking them for their kindness.

Clinical Aspect.

The following account of the clinical features of this disease is based upon nine cases in the wards of the National Hospital during the last three years. A *post-mortem* examination was made in seven of the cases. In the remaining two the diagnosis, although not established by pathological investigation, appears certain. One of these patients died shortly after leaving the hospital, but there was no opportunity for examination, and the other still remains in the hospital.

Added to the detailed clinical and pathological account in the appendix are three other cases, two of which are at present in the National Hospital, and the diagnosis of an early stage of combined degeneration seems highly probable, and a third, probably of the same nature, in which recovery has taken place.

In the first of these series of cases (No. 1) which came under our observation the symptoms were peculiar and striking, and the correct diagnosis was not made during life. In the remaining cases the aspect and course of the disease were so similar to those of the first case that a definite diagnosis was made and was confirmed by subsequent *post-mortem* examination.

So far as we may argue from these nine cases the clinical picture of the disease except in its earliest stage is very definite, and presents features which distinguish it from other affections of the spinal cord. The course of the disease almost always tends to a fatal issue. The changes in the clinical features which occur in the course of the malady are striking, and may be divided into three stages, separated the one from the other by abrupt transitions and by a marked change in the symptom complex; this constituting perhaps one of the most striking clinical features of the affection.

The three stages of the disease indicated may be summarised as follows:—

(1) A stage of slight spastic paraplegia with slight ataxy and marked subjective sensations in the lower limbs.

(2) A stage of severe spastic paraplegia with marked anæsthesia of legs and trunk.

(3) A stage of complete flaccid paraplegia; absent knee-jerks; absolute anæsthesia; rapid wasting and loss of faradic excitability in the muscles of the paraplegic region; increase of superficial reflex excitability; absolute incontinence of both sphincters and œdema of the lower extremities and trunk.

Though an anæmic state has hitherto held an important place in the symptomatology of this disease, and by some authors has been placed in important causal relation with

the spinal cord lesions, we have not included this symptom in the foregoing summary of important symptoms, for the reasons that some of the most typical cases presented no anæmia throughout the whole course of the disease; others presented anæmia only late in the disease, when great general emaciation came on; while in other cases anæmia was an obtrusive symptom from the first, and preceded the manifestation of nervous symptoms by many months.

Repeated examination of the blood in the anæmic cases failed to reveal the alterations found in pernicious anæmia. The changes found were such as occur in cases of secondary anæmia. As regards the causal relation of this disease with pernicious anæmia it may be pointed out that according to the recent opinions of the highest authorities on the subject,[1] a diagnosis of pernicious anæmia arrived at from the character of the blood elements alone is quite unjustifiable.

Etiology based upon the Observation of Seven Cases.

Age.—The disease appears in the fourth and fifth decades of life. The average age of the patients was forty years, the youngest being thirty years old, and the eldest being forty-nine years old.

Sex.—Women seem to be rather more commonly affected than men. Four of the seven cases were females, and three were males.

Heredity.—A slight family history of nervous disease was present in two cases. A marked tubercular family history was present in four cases. Acute rheumatism in three cases, and a history of cancer in two.

Other Factors.

These patients had been, without exception, strong and healthy till a short time before the symptoms became

[1] S. Coupland, "Pernicious Anæmia," Allbutt's "System of Medicine," vol. v., p. 504.

manifest. Four of them had a definite history of syphilis, and in two only could this be excluded with comparative certainty. There had been alcoholic excess in three of the cases, and prolonged suppuration in three others (pyonephrosis, chronic cystitis, and chronic bronchitis). In two cases the symptoms first appeared after pregnancy. Two of the patients lived in adjoining houses in the same street. All the patients were in comfortable circumstances, and no connection could be traced between the disease and acute illness or emotional disturbances.

The onset of the disease was in most cases slow and insidious, and could not be attributed to any immediate exciting cause. In the most acute cases, however, the symptoms came on rapidly, and were ushered in by headache, vomiting, pyrexia, and malaise. Where anæmia had preceded the appearance of nervous symptoms, faintness, languor, palpitation, and irregular pyrexia were the symptoms which brought the patient under the notice of the physician.

The earliest manifestations of implication of the nervous system were subjective sensations in the lower extremities; numbness, a feeling of stiffness, and sometimes tingling. These symptoms were often so slight that it was many months before the patient sought medical advice, but once having appeared they were constant, and showed no tendency to disappear. Soon after these sensory manifestations, signs of slight spasticity and ataxy developed; the legs were clumsy and felt stiff and cold, and there was generally some dragging of the feet in walking. There was at this period of the disease no involvement of the cranial nerves, no girdle sensation, and no sphincter trouble. The signs present at this time were simply an increase of the deep reflexes in the lower extremities, the extensor response in the plantar reflex, and very slight loss of sense of passive position in the lower extremities. Similar symptoms and signs appeared in the upper extremities, generally at a later date than in the lower limbs, but sometimes coincidently, and the clumsiness of the upper limbs was first noticed by the patients in the act of writing.

The clinical picture was one of slight ataxic-paraplegia, and this constituted the first stage of the disease.

Whether the course of the disease was rapid, as in Cases Nos. 2 and 6, where the duration of the illness was four and three months respectively, or chronic, as in Cases Nos. 5 and 9, this stage usually occupied from a half to three-quarters of the whole duration of the illness.

The transition from the first to the second stage was usually abrupt, and was marked by the loss of ability to stand or walk, and by considerable loss of sensibility, to all forms, in the legs and lower part of the trunk. In five of the cases the change occurred in the course of a single night, and the patients, having gone to bed able to walk fairly well, found themselves unable to stand on getting out of bed in the morning. The inability to stand and walk was owing to loss of sense of position, and not to any marked loss of motor power, for this was quite good in some cases. Throughout the second stage the power of movement, as a rule, steadily declined, but was not completely lost in any muscle until the third stage—that of flaccidity—was reached. There were, however, two cases in which there was no marked loss of power until the stage of flaccidity was reached, and one in which the legs became completely paralysed, though still spastic. The muscles were rigid, and exhibited no marked wasting, and their electrical excitability remained normal. The most characteristic sign of the second stage was the rapid development of anæsthesia. Sense of passive position was absolutely lost in the lower limbs, and much impaired in the hands, which usually presented tabetic athetosis. Other forms of sensibility were impaired equally and in an increasing degree. The anæsthesia of the skin was always of peripheral distribution at first, appearing over the feet and hands; but as it gradually extended upwards it became segmental in distribution, and its upper limit upon the trunk was always a segmental limit, sharply defined. The highest level to which the anæsthesia has reached in any of the cases has been the upper limit of the sixth cervical root area (plates i. and ii.). In its progress upwards it may be limited for a

PLATE I.

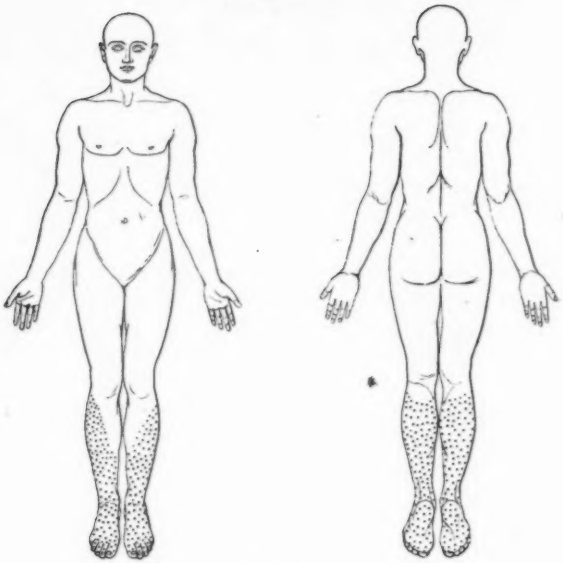


FIG. 1.

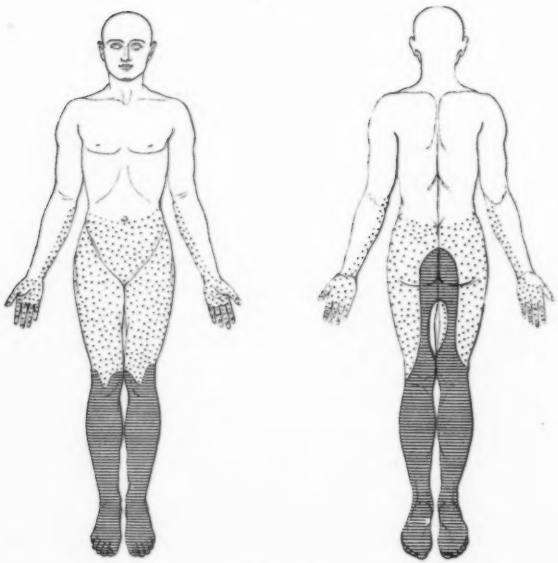


FIG. 2.

FIG. 1.—An early stage in the anæsthesia. Case No. 8.
FIG. 2.—Anæsthesia early in the flaccid stage. Case No. 4.
(The dotted areas represent partial, the lined areas complete, loss to all forms.)

PLATE II.

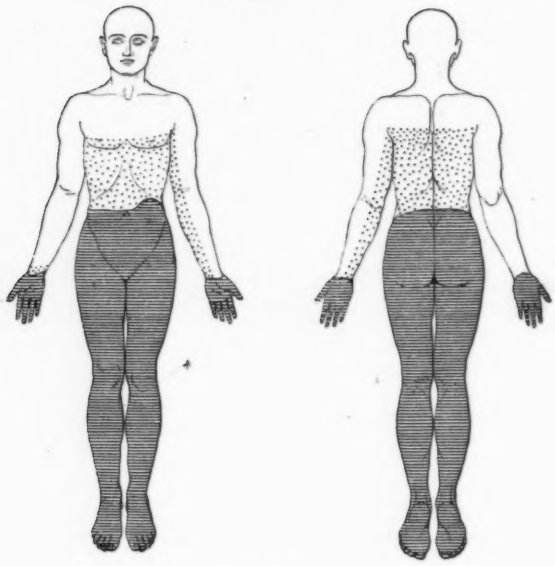


FIG. 1.

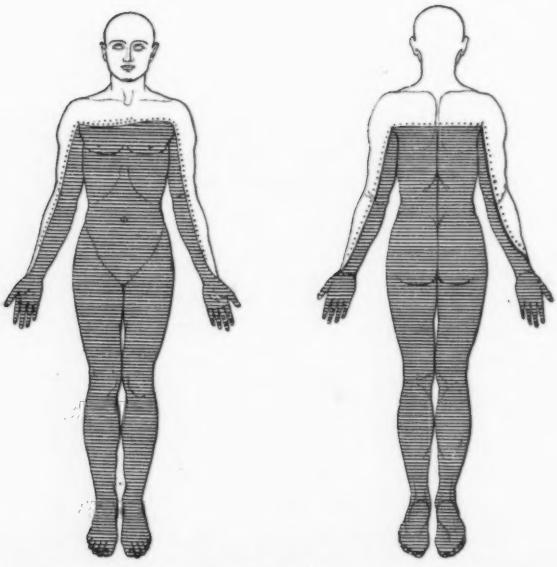


FIG. 2.

FIGS. 1 & 2.—Two late stages in the anæsthesia of Case No. 1.
(The dotted areas represent partial, the lined areas complete, loss to all forms.)

long time to a certain segmental level, and then suddenly encroach for several segments higher, and over the newly-involved area may show marked remissions and exacerbations in its progress to complete anæsthesia. Anæsthesia dolorosa and delay amounting to as much as fifteen seconds has been met with.

The lower lumbar and first sacral areas were always affected before the lower sacral and upper lumbar areas, and the lower cervical segments before the upper thoracic segments.

A girdle sensation in the lower thoracic region was common at this stage, and severe lightning pains in the lower extremities were frequent. A prominent feature of all the cases has been a severe constant dragging pain beneath the lower costal margin, always unilateral; in some cases on the right side and in others on the left.

Attacks of severe intercostal pain on one side were followed by herpes in two cases and in a third by a cutaneous hæmorrhage exactly limited to a nerve-root distribution (plate ix., fig. 1). Similar cutaneous hæmorrhages have been observed in cases of tabes dorsalis by Strauss [1] and others.

In this stage the mental faculties were not affected, and the special senses were found to be normal. Optic neuritis was not present, but in two of the anæmic cases multiple retinal hæmorrhages were found.

The cranial nerves were affected in some cases. Reflex iridoplegia was never present. Many of the cases presented slight nystagmus on extreme lateral deviation of the eyes. Weakness of the external rectus muscle with corresponding diplopia was present in two cases, and in one of them it was bilateral. Slight unilateral facial paresis was present in one case, and marked unilateral paresis and ataxy of the larynx, with alteration of voice, was present in one case.

The sphincters were in this stage often unaffected; in some cases there was slight incontinence, and in one case only complete incontinence. Considering the depth of the

[1] Strauss. "Des ecchymoses tabétique à la suite des corses de douleurs fulgurantes," *Acad. de Neurologie*, 1881.

anæsthesia, this condition of the sphincters was remarkable, and contrasted very strongly with the absolute incontinence always present in the third stage.

Trophic changes were not observed.

Both the superficial and deep reflexes were increased and the jaw-jerk and foot clonus were obtainable. A marked extensor plantar response was present in every case.

During this stage the general condition of nutrition may be good. In the patients with anæmia there were superadded the symptoms of that condition. Both the anæmic and the non-anæmic patients were subject to irregular elevations of temperature and symptoms of dyspepsia.

The length of this stage of the disease has varied in the different cases from three weeks to six months, but it was usually short, and occupied less than one-sixth of the whole time of illness. The average duration of this stage in the cases which have up to the present time proved fatal was five weeks.

The transition from the second stage—that of spastic paraplegia—to the third stage—that of flaccid paraplegia—occurred rapidly in the course of a few days, and was marked by the development of its following succession of symptoms in the lower extremities:—Absolute flaccid motor paralysis; absolute anæsthesia; complete incontinence of the sphincters; loss of the deep reflexes; rapid wasting of the muscles, with loss of faradic excitability; and œdema of the legs and trunk.

This change in the clinical picture occurred in most of the cases while they were under observation in hospital, and it was accompanied by a marked change in the general condition, malaise, drowsiness, anorexia, and general asthenia, becoming evident, and when anæmia was present, it became much increased. Pyrexia was always associated with the event. The accompanying temperature chart from Case 3 shows the behaviour of the temperature in all the cases in which the transition from the second to the third stage was observed.

The lower extremities, which before had been spastic

PLATE III.

FIG. 1.—The right upper extremity of Case No. 7 when admitted.

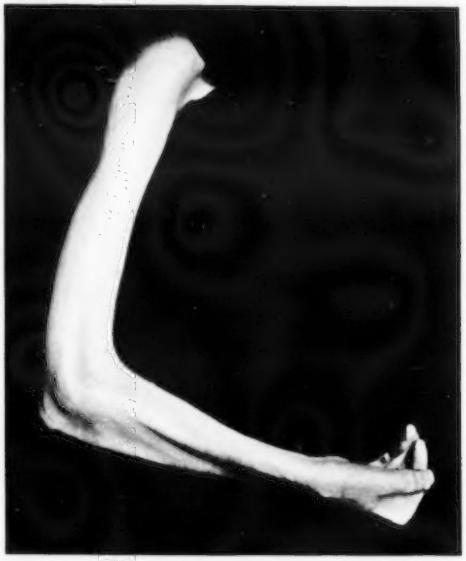
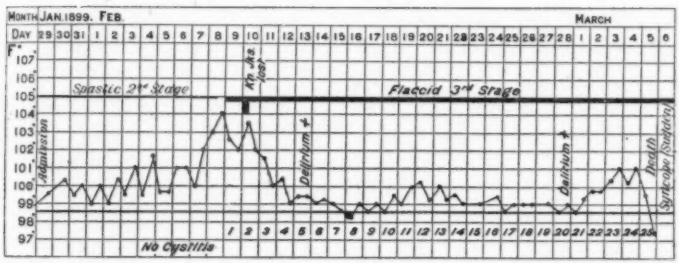


FIG. 2.—The same limb three days before death, showing the extreme muscular wasting.

with reflex spasms, epileptoid spasms, and increase of the deep reflexes, in the course of twenty-four hours became absolutely paralysed, the spasticity giving place to complete flaccidity with marked hypotonicity. The foot clonus was no longer obtainable, and the knee-jerks gradually becoming reduced to mere flickers upon reinforcement, were finally lost about four days after flaccidity had set in. Accompanying this flaccidity was the most striking alteration of the electric excitability, the faradic excitability rapidly falling almost to zero, and the galvanic excitability being much reduced, sometimes with and sometimes without a polar change. The diminution of faradic excitability was observed directly



Temperature Chart of Case 3.

the flaccid condition had set in. That the early change in the electric excitability was not due to the severe œdema of the subcutaneous tissues having insulated the deeper tissues was proved by the employment of sterilised needle electrodes plunged deep into the muscle, the condition of complete anæsthesia of the part allowing of this procedure. The muscles wasted rapidly. In the lower limbs and trunk the wasting was general, but in the upper extremities the wasting, which generally appeared later than in the lower extremities, affected first the intrinsic hand muscles and then the ulnar flexors, radial flexors, extensors of wrist, extensors of elbow, supinati, and fifth cervical group, in that order. This wasting continued throughout the third stage

progressively affecting fresh muscles in an upward direction until, in the cases where the third stage was prolonged, there was extreme atrophy of all the observable muscles of the body, except those supplied by the cranial nerves (see plates 3 and 4).

The trunk muscles, with the onset of the third stage show complete paralysis below a segmental area, usually the ninth dorsal. Beevor's sign was well marked in all the cases (*i.e.*, the shifting upwards of the umbilicus in the attempt to sit up). Subsequently the upper abdominal and spinal muscles, the lower intercostals, and, in some cases, the diaphragm became completely paralysed.

With the exception of single instances in which paresis of the external recti, or of the face on one side, or of the larynx on one side, were met with, no paralysis of muscles supplied by the cranial nerves was noticed, nor were the neck muscles or the infrahyoid muscles affected.

The anæsthesia of the lower extremities and lower trunk rapidly became absolute, and the anæsthesia rose segment after segment; first relative, then slowly becoming absolute. In most cases the anæsthesia reached as high as the first dorsal segment before death, and in two cases it reached the sixth cervical segment (see plate ii.). Girdle pains, lightning pains, and paræsthesia were no longer complained of, but the heavy pain beneath the costal margin persisted to the end. With the onset of the flaccid stage the sphincters became in every case completely incontinent, but showed some reflex contraction to the usual tests. Cystitis occurred in several cases, but it was readily amenable to treatment, except in the cases with a long final stage. In these cases pyelonephrosis occurred. One of the most prominent symptoms following the change to the flaccid stage was the rapid appearance of much soft translucent œdema in the lower extremities and lumbar region. The œdema was much influenced by gravity, and could be readily removed from the feet by raising the legs. Becoming most marked on the fourth day of the flaccid stage, it showed remissions and exacerbations, and disappeared finally after about fourteen days.

PLATE IV.

FIG. 1.—The right lower extremity of Case No. 7 when admitted.

FIG. 2.—The same limb three days before death, showing the extreme muscular wasting.

Acute œdema of one arm, preceded by intense pain and lasting three hours, was observed twice in one case; but with this exception, no œdema was observed above the lumbar cushion. This symptom was present to a marked degree in every case. At this period signs of mental deterioration and disturbance appeared; drowsiness, childishness, nocturnal delirium, and varied delusions were common, and in one case there was prolonged maniacal delirium. Repeated convulsive attacks were noticed in three cases. The spasms were of a fine clonic nature, and affected the limbs only, and chiefly the periphery of the limbs. One of the patients (who only had two attacks) lost consciousness during the attacks, but in the other cases this did not occur.

The convulsions were strikingly like those produced in some people by the administration of chloralose.

The condition of the cranial nerves did not alter during this stage. In some of the patients, towards the end of the illness, the pupils were small, with loss of the cocaine reaction (paralysis of cervical sympathetic).

The abdomen was invariably retracted.

Trophic changes in the skin, similar to those seen in neuritis, occurred in the extremities, and the patients, notwithstanding the utmost care, developed severe bedsores.

The deep reflexes were lost with the onset of the third stage, while the extensor response in the plantar reflex remained marked, and this combination of the signs of posterior and lateral tract involvement was found most valuable in the diagnosis of cases seen for the first time in the third stage of the disease. Case No. 8 came to the hospital at the beginning of the third stage, with incomplete flaccid paralysis of the legs, extreme ataxy, absent knee-jerks, and anæmia. There was a history of syphilis, and the case had been diagnosed as "tabes." The presence of the extensor response was not in accord with the diagnosis of tabes. This case was published in "An Investigation upon the Plantar Reflex," BRAIN, vol. lxxxvii., and it was then submitted that this alteration of the plantar reflex justified a diagnosis of postero-lateral sclerosis. Though there was no pathological verification in this case, the fact

that she died three weeks later, with all the symptoms here described as typical of the third stage of combined degeneration, and that her own medical attendant subsequently furnished us with her earlier clinical history—one of spasticity and ataxy, foot clonus being present to within a few days of admission—places the value of this sign in this case beyond doubt.

A most remarkable fact, considering the wasting of the lower extremities, is that the general superficial reflex excitability of the skin of the lower extremities remains greatly exaggerated till quite late in the third stage.

The third stage, as a rule, lasted about six weeks, three weeks being the shortest period, and death occurred either from sudden syncope or respiratory failure. Two cases, however, lived five months and nine months respectively after the onset of the flaccid stage; but in these cases the onset of the flaccid stage was just as severe and the symptoms for the first few weeks quite similar to those in the more rapidly fatal cases. After reaching a condition in which death was hourly expected, these patients rallied a little and lingered a long time in a drowsy state of low vitality, with no fresh development of symptoms except progression of the muscular wasting and general emaciation. One of these patients would certainly have died in the eighth week of flaccidity of an attack of respiratory failure but for the use of artificial respiration and stimulants. The other case was aroused from a severe syncopal attack by powerful stimulants, without which it seemed probable that he would have died at a similar period. In the condition of mental and physical paralysis, profound anæmia, general emaciation, and sepsis in which these patients lingered for many weeks, it was difficult to conceive how life was maintained from day to day.

A remarkable feature of the cases was the absence of any improvement of the nervous symptoms under treatment. From the first appearance of the disease to the fatal event, the tendency was for the symptoms to increase, sometimes halting, sometimes progressing rapidly, but never showing any remission. Under treatment the general health and the

anæmia improved markedly in some cases, but the nervous symptoms never.

All the patients, in whatever stage they came under observation, showed irregular pyrexia, and this entirely apart from any anæmic state; for the non-anæmic cases presented it markedly, and apart from the presence of any obvious cause, such as cystitis, bedsores, &c. The temperature was often subnormal, and the range of upward excursion did not exceed 102·5° F., and was usually about 100·5°F.; with the transition from the spastic to the flaccid stage there was always a marked increase in the pyrexia, lasting several days (see chart).

Though the passage from the first to the second stage was not actually observed in any case, it was ascertained with certainty in two of the cases from the private medical attendant of the patients that marked pyrexia had been present at that time.

In the clinical picture of this disease there remains to be discussed the anæmia, which may be considered under the following headings:—

(1) The anæmia preceded the appearance of the nervous symptoms, and was marked throughout Cases Nos. 3 and 4.

(2) Its date of appearance was coincident with that of the nerve symptoms, and increased with them. Case No. 7.

(3) It was only present at the end of a prolonged third stage, when emaciation became extreme. It was then profound. Case No. 1.

(4) There was no anæmia during the whole course of the illness. Cases 2 and 5.

(5) The blood was not examined. Case No. 6.

The characters of the blood were those of a secondary anæmia. The red blood-corpuscles were well shapen, except in Case No. 4, when the anæmia was most profound. A few small dark-coloured cells were generally present. Nucleated red blood-cells were only found in one case, and then in very small numbers. Gigantoblasts and microblasts were not found.

The number of leucocytes were increased both relatively to the red-cells and absolutely. The number of lymphocytes

were relatively increased in all cases, and that of the coarse oxyphile-cells diminished. In three cases large oval-cells with reniform nuclei were found in small numbers.

The hæmoglobin was diminished in greater proportion than were the corpuscles. The diminution in number of corpuscles was most marked towards the end of the illness; for an instance in Case 4.

Two months before death—Hb. 56 per cent., R.B.C.'s 4,000,000.

Three days before death—Hb. 18 per cent., R.B.C.'s 800,000.

There was nothing in the blood of any of the cases in which it was examined to suggest "pernicious anæmia."

Neither the spleen nor lymph glands were palpably enlarged in any case.

Hæmorrhage was uncommon except from the bladder in connection with cystitis, when it was common. It was met with in the retina in two cases, and in the skin in one case, and in these cases it was not repeated. Thrombosis was not met with.

The usual symptoms of anæmia, air hunger, lassitude, syncopal attacks, &c., were marked.

In several cases the anæmia showed marked temporary improvement under treatment with iron and arsenic, but the improvement lasted only a short time.

The other organs of the body presented nothing worthy of special notice.

The clinical picture in three tableaux here set forth has been followed by all of these cases up to the present time fatal. The cases varied as regards the anæmia and the length of the illness. But if the slightness of the symptoms in those patients presenting a long first stage, and the conditions under which the third stage was prolonged in Cases 1 and 7, the regularity of the course of the disease as regards time is most striking.

Most of the patients have died within four months of losing ability to walk. The duration of the illness varying between three months and thirty months averages under nine months.

The following cases, which are included in the appendix, presented the clinical picture of the malady, but have not been verified.

Case No. 9, at the present time under the care of one of us (J. S. R. R.) at the National Hospital, we regard as an instance of the disease, and it suggests that in some cases the latter stages of the disease may be more chronic, especially the second stage, which in the other cases has been short, and in this case complete anæsthesia, complete incontinence and complete paralysis, with wasting of the muscles and diminution of faradic excitability are present, while the legs are very spastic and the knee-jerks increased with double foot clonus, that is, in the second stage, whereas, in the other cases, such symptoms only appeared with the onset of flaccidity and the loss of the deep reflexes.

Three other cases are recorded in the appendix. The first, No. 10, is submitted as a case of combined degeneration during a prolonged second stage, and the second, No. 11, as a case slowly passing from the second to the third stage. It is suggested that Case No. 12, in which recovery took place, was also of this nature—at all events, it could not be clinically distinguished.

Diagnosis.

The differential diagnosis of combined degeneration, while it is simple in the later stages, presents great difficulty in the early stages. Since few of the cases in which the diagnosis has been verified after death were seen in the first stage, and since the clinical picture of that stage has been drawn almost entirely from the accounts of the patients and their friends (collected with every possible precaution to avoid error), and from the medical attendants of the patients at their own homes, and since no diagnosis of combined degeneration was made at the stage in any of these cases verified after death, we can do no more than point out the probable features that may lead to a correct diagnosis in the first stage.

The importance of early diagnosis is obvious from a point

of view of prognosis, and it is possible that the disease may then be amenable to treatment.

The early clinical picture of combined degeneration, that of slight ataxy and spasticity, resembles closely that of the common paraplegic form of disseminated sclerosis in an early stage. Three of the cases here recorded were examined by competent authorities soon after their symptoms commenced and the diagnoses made by them, were :—

Case No. 3. Slight spastic paraplegia. Anæmia. ? cause.

Case No. 5. Early disseminated sclerosis.

Case No. 6. ? Early disseminated sclerosis.

In attempting to distinguish these two diseases, careful attention should be paid to the history. The age at which combined degeneration occurs is not the most common for the appearance of symptoms of disseminated sclerosis. The preponderance of subjective sensations in the legs, the absence of the functional manifestations, of exacerbations and remissions of the symptoms, of nystagmus, and of sphincter trouble which are so usual in disseminated sclerosis, and the presence of irregular pyrexia are probably of great importance in the early diagnosis of combined degenerations.

The presence of anæmia in an early case of spastic paraplegia should give rise to a suspicion, but the possibility of chlorosis, associated with disseminated sclerosis in young women, must be borne in mind. A symmetrical affection of all limbs, with slight ataxy and spasticity, preponderating in the legs, is a most important distinguishing symptom of combined degeneration.

In the second stage the diagnosis is more certain. The history of slight symptoms preceding a sudden complete and lasting helplessness of the legs ; the preponderance at first of ataxy over loss of power ; the rapidly-increasing anæsthesia, paresis, and spasticity ; the severe lightning pains ; the absence of sphincter trouble as a rule ; the pyrexia and the ænemia, if present, serve to separate the disease from other forms of paraplegia.

In the third stage the diagnosis is easily made from the only diseases which present a symptomatology in any

way resembling that of combined degenerations. These diseases are tabes dorsalis, acute myelitis, polyneuritis, and spinal tumour.

Most of the cases were sent to the hospital for the first time in this stage labelled "Tabes," on account of the flaccidity, anæsthesia, loss of deep reflexes, and complete incontinence. A history of spasticity changing rapidly to flaccidity, the completeness of paralysis and anæsthesia, the pyrexia, the œdema of the legs, the rapid muscular wasting and loss of faradic excitability, and that sure sign of involvement of the pyramidal system—Babinski's extensor response in the plantar reflex—at once excludes tabes dorsalis. Moreover, the Argyll-Robertson pupil was never present. In one case bilateral sympathetic paralysis had been described as "slight bilateral ptosis, marked myosis, and reflex iridoplegia." The sudden onset of complete paralysis and œdema resembles the onset of acute myelitis, but the preceding history will at once distinguish the two conditions.

A tumour pressing on the spinal cord, and giving rise in order to slight and severe spastic paraplegia, and finally to flaccid paraplegia, in some cases produces the picture most nearly approaching that of combined degenerations. The absence of severe root pains preceding the paralysis and the distribution of the physical signs in very unequal degree, in the upper and lower limbs, together with the absence of other distinctive signs of spinal tumour, should prevent an error in diagnosis.

The involvement of all the limbs, with flaccid paralysis, wasting, diminution of faradic excitability, anæsthesia, and loss of the deep reflexes are not unlike the symptoms of peripheral neuritis, but the resemblance is superficial only. The history of a preceding spastic state is incompatible with the diagnosis of polyneuritis. Total incontinence of the sphincters, paralysis of the trunk muscles, anæsthesia upon the trunk, following a root distribution, girdle sensations, and the presence of the extensor response in the plantar reflex are symptoms quite incompatible with a diagnosis of polyneuritis.

Prognosis.

So far as these cases are concerned the certain diagnosis of combined degeneration passes a short sentence upon the patient.

It may be, however, justifiable here to note that a patient of Dr. Ferrier's, at the National Hospital, suffered with a short illness associated with pyrexia, in which he suffered successively with slight ataxic paraplegia, severe ataxic paraplegia, and flaccid paraplegia, with wasting, œdema, and complete incontinence. After remaining flaccid for five days, he rallied from an apparently moribund state, and made a rapid recovery.

This patient is still under observation, and is at work. (Case No. 12.)

Treatment.

It has been already mentioned that under treatment with iron and arsenic the anæmia may improve greatly for a time.

No drugs have been found to influence the nervous symptoms in any way. Mercury, iron, iodide of potassium, arsenic, strychnine, quinine, salicylates, and various animal extracts have been given with no benefit.

MORBID ANATOMY.

The condition of the body at the time of death varied with the duration of the last stage of the disease. When this had been long, the limbs and especially the lower extremities were wasted, and in some cases this was extreme, and the legs had become contracted in the flexed position. In those cases in which the last stage of the disease was of shorter duration, the wasting was not so marked, and in these cases there was often a good deal of adipose tissue, not only over the trunk, but also over the extremities. Bedsores have always been present.

The brain, cerebellum, and pons in most cases appeared perfectly normal, but there was occasionally some wasting of the cortex, with slight thickening of the membranes and

compensatory œdema. The vessels at the base of the brain appeared perfectly normal.

The spinal cord, apart from being slightly wasted (a condition, however, by no means always present) appeared perfectly normal, so far as its external aspect was concerned. There was, however, in one case slight opacity of the arachnoid membrane. On section of the cord, the gray appearance of the degenerated parts was at once obvious, and this became more marked after the cord had been hardened in Müller's fluid, when the sclerosed areas stood out of a lighter colour than the neighbouring healthy tissue.

The lungs have shown various degrees of œdema and patchy pneumonia, but otherwise have appeared normal.

The heart, both in regard to its valves and the condition of its walls, has appeared normal; in one case it was described as fatty. The pericardium has in all cases appeared normal.

The liver was generally enlarged to a slight degree, but showed no marked change; no free iron reaction has been obtained.

The spleen was found enlarged and soft, but the condition seemed to depend on the condition of the bladder and kidneys; for when these were normal the spleen did not manifest the above changes.

The kidneys often showed some change secondary to the condition of the bladder, either septic infarcts or pyonephrosis; in other cases they were either normal or showed slight granular change.

The bladder showed varying degrees of cystitis.

The bone marrow was examined in two cases from the femur, and in the first appeared red and almost diffluent, resembling the condition of the softened spleen; and this was a case in which the bladder appeared fairly healthy; in the second case it was of a more normal appearance, being pale and of the usual consistency. The muscles of the leg showed various degrees of atrophy, in most cases being flabby and very œdematous, but in others being simply wasted. The muscles of the upper extremity were much less affected than those of the lower.

Plate V.

Series of sections from the medulla and spinal cord of Case No. 1.

The last stage of the disease in this case was of long duration, and consequently the amount of sclerosis is greater.

The sections have been stained by the Weigert-Pal method, and show the most marked change in the mid-dorsal region, where the whole of the periphery of the cord is affected, leaving the gray matter and a few medullated fibres in the immediate neighbourhood intact (figs. 4, 5, 6, 7). In the lowest of these, however, the whole of the periphery is not destroyed, a portion of the antero-lateral tract remaining intact (fig. 7).

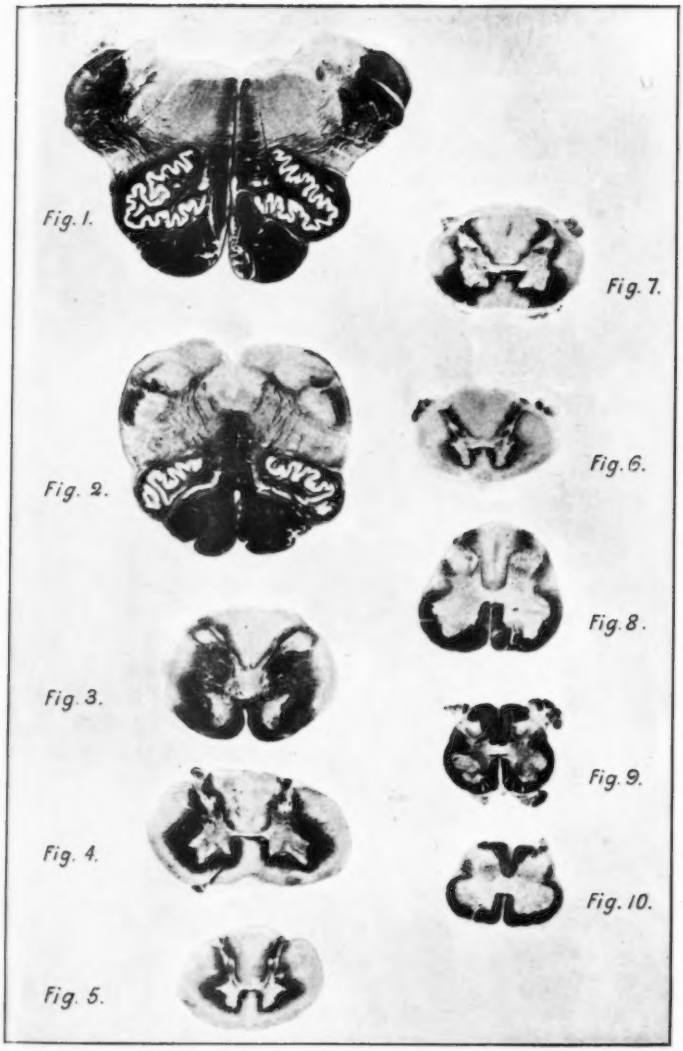
In the lumbar region the disease tends to be limited to the posterior columns and the crossed pyramidal tracts, while in the sacral region, except for some slight affection of the crossed pyramidal tracts, the cord appears normal (figs. 8, 9, 10).

In the lower cervical region the destruction of the cord is still extensive, involving the periphery, but leaving a wider area of normal medullated fibres round the gray matter (fig. 4).

At the level of the first cervical segment (fig. 3) the most marked degeneration of the cord exists in the posterior columns and direct cerebellar tracts, but it is not limited to these.

In the medulla (figs. 1 and 2) the pyramids appear normal, but there is obvious degeneration in the region of the direct cerebellar tract and of the posterior column nuclei.

PLATE V.



CASE No. 1.

Microscopical Appearances.

The stress of the disease fell upon the mid-dorsal region of the cord, and therefore it will be convenient to commence with a description of the condition found in this region, and subsequently to pass to other portions of the cord. On examining a section of the cord taken from about the level of the sixth or seventh dorsal nerves stained by the Weigert-Pal method, it was at once apparent that there had been very marked destruction of the white matter of the cord all round the periphery, leaving the gray matter and a small area of white matter immediately surrounding it perfectly normal (see plate v., figs. 5 and 6, and plate vi., figs. 6 and 7); and it was apparent also that the destruction was not in any way limited to the long tracts of the cord, but affected the endogenous and exogenous fibres alike—in fact, all that was not in close proximity to the gray matter.

The posterior columns, which are generally most affected, may be completely sclerosed except for a small area in immediate contact with the middle third of the posterior horns.

If from this point in the mid-dorsal region the process was traced up the cord, it was found that the general destruction gradually became less, and, instead of affecting all tracts alike, tended to limit itself to the posterior columns (the columns of Goll being more affected than those of Burdach), the dorsal and ventral cerebellar tracts; and to the crossed pyramidal tracts (plate v., figs. 3 and 4, plate vi., fig. 3). But even in the cervical region, although these may be the most affected areas of the cord, yet the disease was by no means limited to them, for scattered degenerate areas were also present, a favourite situation for these being in the ventral region of the cord in the position occupied by the direct pyramidal tracts and the neighbouring ground bundles (plate v., fig. 4).

The destructive lesion was found as high as the upper portion of the medulla, but degenerate fibres could be seen by the Marchi method in the pyramidal tracts as high as the mid-region of the pons, and in the upper portion of the ventral cerebellar tract in the velum.

Plate VI.

Series of sections from the medulla and spinal cord of Case No. 2.

The last stage of the disease in this case was comparatively short, lasting only about three weeks.

The sections have been stained by the Weigert-Pal method, and show the most marked degeneration in the mid-dorsal region. In this region (figs. 5, 6, 7, 8) there is degeneration both of the posterior and antero-lateral tracts, leaving the ventral portion of the cord unaffected except for a few scattered patches.

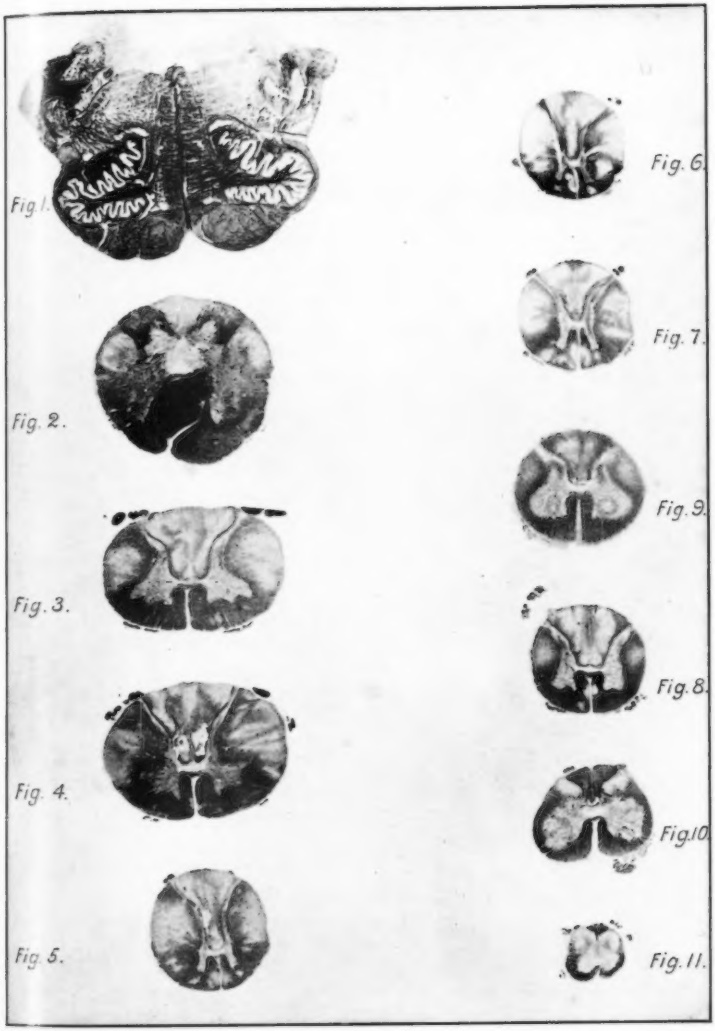
In the lumbar region (fig. 9) the degeneration is almost limited to the posterior columns and the crossed pyramidal tracts, while in the sacral region (fig. 10), except for some slight change in the crossed pyramidal tracts, the cord appears normal.

In the cervical region (figs. 3 and 4) there is marked degeneration in the neighbourhood of the crossed pyramidal tract and the posterior columns, leaving the ventral portion of the cord almost normal.

In the medulla (fig. 2) the pyramids appear normal, and the only degeneration visible by this method is that seen in the funiculus gracilis.

Although the degeneration has been described in certain tracts, it will be noticed that it is by no means limited to the strict margins of the tracts, and also that the degeneration occurs in patches, but that the margins of these never have the sharp edge that is commonly seen in disseminated sclerosis.

PLATE VI.



Case No. 2.

The upper portion of the pons, the internal capsule, and the cortex of the brain appeared perfectly normal.

On passing to the condition of the cord below the mid-dorsal region, it was found that the diffuse destructive process steadily tended to diminish as the lumbar region was reached, and here it was usually found that the degeneration was limited to the crossed pyramidal tracts with some patchy destruction in the posterior columns, and possibly also in the ventral region of the cord (plate vi., fig. 8). In the sacral region the degeneration was almost entirely limited to the crossed pyramidal tracts, though in some instances patchy degeneration was present in the posterior columns also.

With regard to the condition as seen by the Marchi method, the same features as above described were observable, but it was found that the areas in which degenerate fibres could be seen were considerably wider than those which the Weigert-Pal method had indicated, and these recently degenerate fibres were present in largest numbers in that part of the affected area which bordered on the healthy white matter interposed between this and the vacuolated area to be described below. Degenerate fibres were also found scattered in the otherwise healthy white matter, in the vacuolated region, and to a much less extent or not at all in the sclerosed areas (plate vii.).

Lissauer's tract appeared, for the most part, normal on examination both by the Weigert-Pal and Marchi methods. In some cases it was rather pale as seen in sections prepared by the former method, but when compared with the normal tract the difference was not striking, and the absence of any recently degenerated fibres also seemed to support this view. Even in the mid-dorsal region, where the periphery of the cord was extensively affected, this tract, together with the apex of the posterior horn, escaped destruction.

There were obviously two distinct processes at work in relation to the alteration found in the spinal cords of these cases.

(1) A focal destructive lesion.

(2) A system lesion.

Plate VII.

Series of sections from the medulla and spinal cord of Case No. 5 stained by the Marchi method. The sections have been drawn under an Edinger's projection apparatus.

In the medulla the most marked degeneration is seen in the direct cerebellar tracts and to a less extent in the pyramids (fig. 1).

In the cervical region (figs. 2, 3, 4) the areas of most marked degeneration appear to be the columns of Burdach, the pyramidal and direct cerebellar tracts, although the degeneration is by no means limited to these. The apparent absence of degeneration in the columns of Goll is accounted for by their complete sclerosis. The areas of degeneration are wider than those seen when similar sections are stained by the Weigert-Pal method.

In the dorsal region (figs. 5, 6, 7) the area of degeneration is wider, leaving only a small band without any degenerated fibres in the antero-lateral tracts.

In the lumbar and sacral regions (figs. 8 and 9) of the cord, degenerated fibres can be seen in the posterior columns, in the situation of the crossed pyramidal tracts, and in the ventral region of the cord.

PLATE VII.

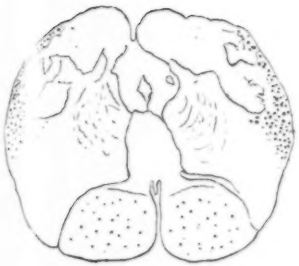


Fig. 1.

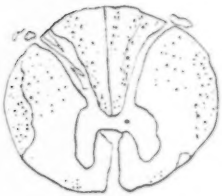


Fig. 2.

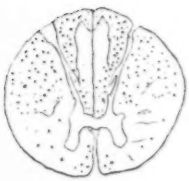


Fig. 5.

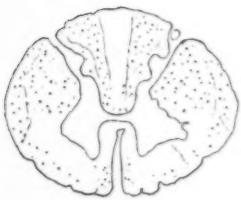


Fig. 3.

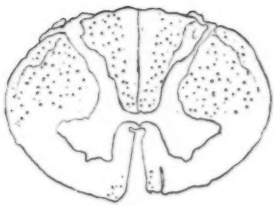


Fig. 4.

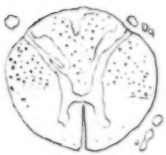


Fig. 6.

Fig. 7.

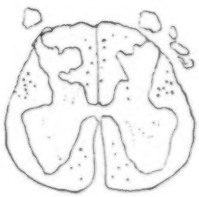
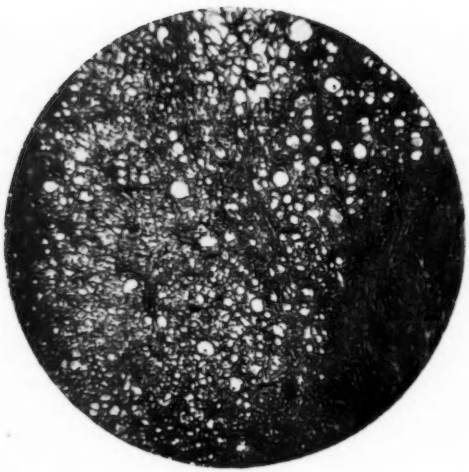


Fig. 8.

Fig. 9.

CASE No. 5.

PLATE VIII.



Transverse section of the spinal cord from the mid-dorsal region to show the vacuolated condition which occurs in these cases from the swelling of the medullated sheath and subsequent absorption of the products of degeneration.

The normal gray matter and some healthy fibres are seen to the left of the field, and some vessels with thickened walls can be seen in the vacuolated area. Magnified 43 diameters. The largest space seen in the centre of the field measures ·07 mm. in diameter. The normal medullated fibres in the same field measure rather less than ·01 mm.

With regard to the first, on examining the margin of the patches of degeneration, it was found that the earliest process that took place was swelling of the medullated sheaths, the axis-cylinders remaining apparently unaltered. The next step was that the swollen sheath underwent fatty degeneration, and this in turn became absorbed, and at the same time the axis cylinders disappeared, a space being thus formed, simply surrounded by the connective tissue of the cord. This space was often of considerable size from the fact that the individual spaces became fused into one another, and in those portions of the cord where the destruction had been most acute nothing was left but the connective tissue which formerly supported the now atrophied fibres forming the vacuolated areas above alluded to and figured in plate viii. In certain cases in which the condition had existed for a considerable time, or in those portions of the cord in which the disease was of longest standing, a considerable amount of fibrous tissue had become deposited in and about the loose meshwork, and a dense sclerosis of the cord had occurred in which neither spaces, medullated sheaths, nor axis cylinders could be seen.

As to the second process, viz., the system degeneration, it was found that the long tracts of the cord exhibited a degeneration similar to that which is found after transverse lesions of the cord, that is to say, there was degeneration of the medullated sheaths and axis cylinders and a gradual replacement by connective tissue giving rise to a definite sclerosis of the cord. The two processes merged into one another so closely that it was often impossible to say which was the focal lesion and which the system lesion, but as a general rule the farther from the mid-dorsal region the more easy it was to distinguish what appeared to be system degeneration from that due to focal changes, so that in the cervical region the system degeneration became more apparent in the afferent tracts, while in the lumbar region it was more evident in the efferent tracts, but it is not to be supposed that the change was limited to afferent or efferent tracts in either region, for extensive degeneration was found in the pyramidal tracts even as high up as the medulla,

while, on the other hand, similar changes were found in the posterior columns in the lumbar region.

The gray matter was practically normal. There were no degenerate areas present, nor were there any hæmorrhages, and, moreover, the vessels were neither thickened nor engorged.

The cells of the anterior horns and of Clarke's columns were for the most part normal; in certain sections of the cord, however, there were possibly rather fewer cells than normal, but those that remained were well stained. The nucleus and nucleolus were normal, as were the cell processes and the chromophilic granules, both as regards their arrangement and their staining; many of the cells were however extensively pigmented, this pigment being apparent not only by the Marchi method, but also by the Nissl method.

The anterior nerve-roots appeared normal both to the Marchi and Weigert-Pal methods, and this even in the dorsal region, where they lay in close contact with the degenerated areas within the cord.

The posterior nerve-roots and the posterior root ganglia appeared normal, although here again the cells contained a considerable amount of pigment. In one case, however—No. 7—in which a subcutaneous hæmorrhage had occurred in the area of skin supplied by the seventh left posterior root (plate ix., fig. 1), a cyst measuring 3 mm. in diameter and filled with clear fluid was found (plate viii., fig. 2). Many of the cells of this ganglion had undergone considerable atrophy, although others appeared perfectly normal. There was also an incision of the connective tissue between the cells. The vessels of the cord in the affected areas were engorged and their walls thickened, but there was no actual thrombosis. In the unaffected areas, however, the vessels were neither engorged nor thickened. An exceptional condition was, however, met with in one case in which the middle coat of the vessel appeared to have undergone a hyaline change. There was no obvious thickening of the membranes even over the areas in which the sclerosis of the cord was most marked.

PLATE IX.

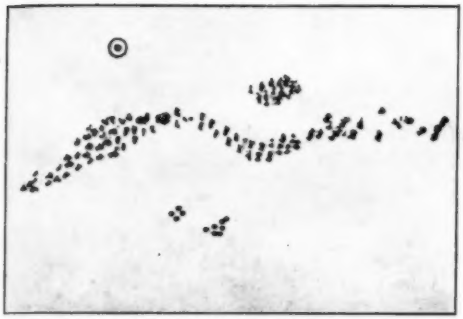


FIG. 1.

Subcutaneous hæmorrhage over chiefly the seventh left thoracic root area. The left limit of the figure is the middle line of the body in front, the right limit is the posterior mid-line. The seventh dorsal spine and nipple are indicated.

(*Traced from the body upon paper and reduced.*)

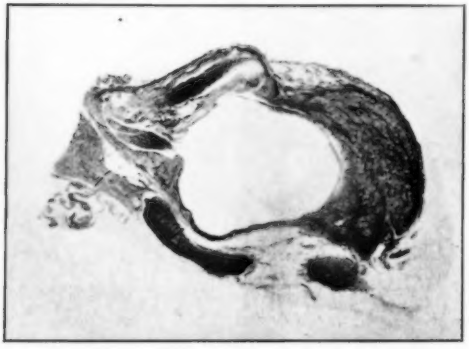


FIG. 2.

Section through the seventh left thoracic posterior root ganglion showing a cyst occupying the centre of the ganglion (case 7). The cyst measured 3 mm. by 4 mm. and was filled with a clear fluid. The walls of the cyst are composed of two coats, an outer of closely packed and an inner of loose connective tissue. Many of the cells of the ganglion are normal; altered and shrivelled cells are also present.—Magnified six diameters.

Nerves.—Various peripheral nerves have been examined, and in most of the cases they were found to be normal or showed only very slight changes, either by the Marchi or Weigert-Pal methods. In one case (No. 1), however, there was very considerable degeneration of the nerve-fibres —a change that not only occurred in the larger nerve-fibres, but which also involved the finer branches of the nerves within the muscles, and which appeared to affect not only the motor nerves but also those of sensory origin within the muscle-spindle. The degeneration of the nerves would seem to be a late manifestation of the disease, as this patient lived a long time after the disease was far advanced.

Muscles.—The condition of the muscle-fibres in these cases varied considerably, although they all showed atrophy; the degree to which this had taken place differed to a very great extent. In the most extreme case the fibres had become so reduced in size that they had lost their striation, and measured only ·004 mm. in diameter, and there was in this case a corresponding increase of the connective tissue (plate x., fig. 1). It was interesting to note that although the atrophy of the muscle-fibres had become so extreme, yet many of the finer nerve-fibres in the immediate neighbourhood were, to all appearances, perfectly normal. On the other hand, in the cases in which the atrophy was not so marked (and these form the greater proportion of the cases) it was found that the extent to which the muscle-fibres were reduced in size was such, that instead of measuring from ·06 to ·08 mm. in diameter, they measured on the average less than ·04 mm., and assumed a rounded instead of the polygonal shape commonly seen in muscle cut in transverse section after hardening (plate x., fig. 2). In a small number fat could be seen within the muscle-fibres; these were always fibres of small size, and usually measured from ·03 to ·02 mm. in diameter. This fatty degeneration of the fibres was rather the exception than the rule. There was no evidence of any inflammatory process, unless we accept the increase of connective tissue as having this significance; whereas, as above stated, this was sufficiently accounted for by the extreme atrophy which the muscle-fibres had undergone.

Muscle-spindles.—These organs appeared remarkably well preserved, especially when the atrophic condition of the muscle in which they lay was taken into account. The capsule and general appearance of the spindle was normal; the intrafusal muscle-fibres were of normal size, retained their striation, and only a few of them exhibited slight fatty degeneration. With regard to the nerves passing to the muscle-spindle, many appeared normal, and all those examined contained at least one normal fibre; when, however, we consider the large number of nerve-fibres which are normally present in the muscle-spindle, it seemed probable that there had been a certain amount of atrophy of the nerve-fibres even within the muscle-spindle.

The muscle-fibres of the diaphragm appeared normal.

The heart muscle appeared fairly normal; there was no fatty degeneration, but there was brown pigmentation of the fibres, extending from either pole of the nucleus of the fibre; the muscle-fibres did not appear much atrophied, and measured about ·02 mm.

The liver in the cases examined did not give the free iron reaction. There was some fat in the periphery of the lobules of the liver, but not in such amount as to be considered pathological.

The kidneys in those cases in which there had been infection from the bladder showed areas of small cell infiltration; in other cases they appeared normal, or showed slight fatty degeneration in the epithelium of the tubules.

Pathology.

Various views have been advanced as to the ætiology and pathology of the affection; but as these have been fully discussed in a former paper by one of us (J. S. R. R.), we do not propose to do more than epitomise the salient points brought out in that discussion. The spinal cord changes have been variously attributed by different writers to one or other of the following causes:—

PLATE X.

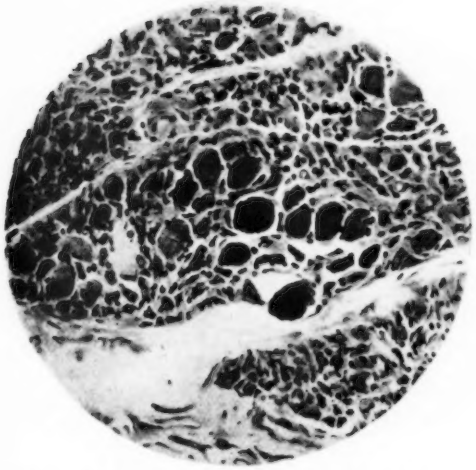


FIG. 1.—Transverse section from the vastus internus muscle of case No. 1, showing the extreme degree to which atrophy may take place. A portion of the muscle has been selected in which some comparatively large fibres remain, but the majority are atrophied to such a degree that they measure less than ·004 mm. The large muscle fibre in the centre of the field measures ·03 mm., *i.e.*, about one-half the diameter of a normal fibre.

There is a very considerable increase in the nuclei between the muscle fibres, but not more than can be accounted for by the fact that the normal connective tissue nuclei are approximated owing to the atrophy of the muscle fibres. Magnified 160 diameters.

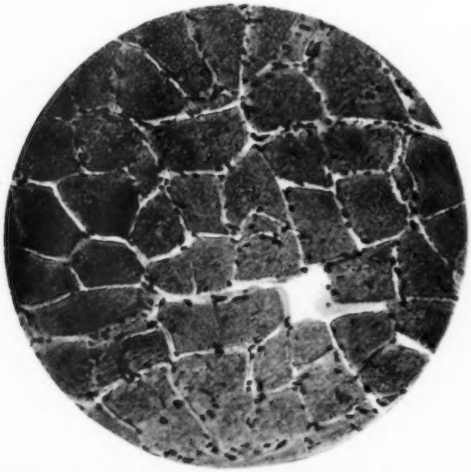


FIG. 2.—Transverse section from a normal vastus internus muscle for comparison with the above. The normal muscle fibres measure about ·06 mm. in diameter. Magnified 160 diameters.

(1) The anæmia frequently found in association with the spinal cord symptoms in these cases.

(2) Multiple hæmorrhages in the spinal cord occurring in association with the anæmia.

(3) Thickening of the walls of the blood-vessels, the vascular change being primary and that in the nerve elements secondary in origin.

(4) An acute myelitis occurring in the earlier stages of the disease, or a disseminated myelitis having a predilection for certain tracts of the spinal cord.

(5) The affection of the white matter secondary to a primary change in the gray matter of the cord.

(6) A toxic agent, which is jointly responsible for the changes in the spinal cord and for the anæmia in those cases in which this symptom is present.

The existence of so many different views on this question must, in part at any rate, be due to the opinions of writers being based on the particular conditions found in the cases which have come under their individual observation, and in greater part probably owing to the confusion that has already been alluded to, and in consequence of which cord changes occurring in the course of severe anæmia have been regarded as identical with the subacute combined degeneration of the cord in which anæmia may be a prominent symptom. A study of our own cases, in conjunction with all the recorded cases that strictly come within the same category does not, it appears to us, admit of such diversity of opinion.

The first point to be considered is what justification there is for regarding the cord changes as due to anæmia; but the objections to this hypothesis are so strong that we do not propose to devote much space to its discussion. Though a marked feature in many of the cases of the disease under consideration, anæmia has not been present, at any rate, to any notable degree in some, while in others in which it has been a prominent feature, the anæmia has not become obvious until some time after the spinal cord affection has manifested its presence by such clinical phenomena as we know indicate disturbance of this part of the central nervous

system. Moreover, although cases of profound anæmia commonly occur, and although a large number of such cases which present the features of the pernicious and other varieties of anæmia have been examined by competent observers, in none of them have there been either clinically or after death the phenomena which characterise the class of case whose pathology we are now considering. Morbid changes have been found in the spinal cord in some cases of fatal anæmia, but in none of them have the changes been in any way comparable to those so characteristic of the group of cases of sub-acute combined degeneration. While dissenting from the view of those who hold that anæmia is responsible for the morbid changes present in the cases of combined degenerations, we are, nevertheless, prepared to admit the possibility that anæmia may play a part in reducing the resistive powers of the nerve elements, thus rendering them less able to withstand the baneful influence of toxins, a property which anæmia may be supposed to share with other debilitating influences and cachectic states. Thus it may happen that anæmia or other impoverished states of the system, themselves dependent on the action of some toxin, may in their turn render the nerve elements more susceptible to the action of the same, or, it may be, some other poison.

The view which supposes the degenerative changes in the various affected tracts of the cord to be due to small hæmorrhages is equally untenable, for no hæmorrhages were present in any of the cases included in our present series, nor could the slightest traces of former extravasations be detected. Even when hæmorrhages have been described as present, they have been too few, too small, and too scattered to possibly account for degenerations affecting tracts symmetrically and in their entirety throughout so large a part of the spinal cord, and producing so profound an alteration as to result in the complete degeneration of certain of them in parts of their course. Moreover, did larger hæmorrhages occur at certain points in the cord so as to interrupt the greater parts of the same tracts on both sides, we should find some evidence of ascending degenerations of certain tracts above such lesions

with their escape, at any rate in part, below them, and of descending degenerations of other tracts below such hæmorrhages with partial or complete escape of the same tracts above them. Not only have no such hæmorrhages ever been met with, but the distribution of the degenerations in the cord quite precludes such a possibility. It is only necessary to remember that in most of these cases the degeneration both in the posterior and lateral columns is most pronounced in the mid-thoracic region of the cord, and that it diminishes in degree and extent in both pairs of tracts as we pass towards the cephalic and caudal extremities respectively.

The hypothesis which, while not regarding the degenerations in the cord as secondary to hæmorrhages, nevertheless assumes that they are of vascular origin in the sense that the degeneration commences in the immediate vicinity of vessels with altered walls, owes its origin to the observations of Nonne and Minnich, who both found areas of degeneration surrounding vessels with altered walls, but who were not dealing with the class of case whose pathology we are now discussing, but with cases of anæmia in which patches of degeneration were met with in the spinal cord. We have found nothing in the appearances of the morbid changes in the cords of our cases to justify the belief that the affection is vascular in origin in the sense that alterations occur primarily in the walls of the blood-vessels, and that the changes in the nerve elements are secondarily induced. That the topographical distribution of the degeneration of the white matter of the cord depends on the vascular distribution, however, there seems to be little question. This will be obvious if it be borne in mind that the blood supply of a given transverse area of the cord is mainly derived from two sources, the anterior median arteries in the anterior median fissure and the peripheral arteries derived from the vessels of the pia mater. The former supply the gray matter of the anterior horns and the white matter bordering on them, and the neck of the posterior horns, including Clarke's columns, while the latter supply nearly the whole of the rest of the white matter of the cord. The distribution of the affection in the white

matter of the cord in these cases of combined degeneration is precisely that of these peripheral vessels. Why there should be the escape of the area of supply of the anterior median arteries is not clear, but this much seems certain, viz., that the affection of regions supplied by the peripheral vessels does not depend on pachymeningitis in these cases, for no such change has been found in any of our present series. This admission that the morbid condition owes its topographical distribution to the vascular supply must not be interpreted as meaning that we are of opinion that the degenerations of the spinal cord are vascular in the sense that they depend on changes in the vessel walls, whose impermeability leads to impoverishment of the nerve elements. That such thickening of vessels occurs, and that when it occurs it cannot fail to affect the nutrition of the parts supplied by such vessels is admitted; but that this is the primary cause of the degeneration of the nerve element is far from our belief. We regard such changes in the vessel walls as have been found as depending on the same cause as the parenchymatous degeneration of the nerve elements, or as resulting from irritative disturbance consequent on the degenerative changes in these; and that the only part played by the vessels in the initiation of the morbid changes in the nerve elements is that of bringing the toxic material to them.

The question of the vascular supply of the cord and its influence on the topographical distribution of the morbid changes is, however, of interest from another point of view. It is tempting to assume that the fact that the most extensive changes are met with in the mid-thoracic cord is due to the fact that this portion of the cord is less well supplied with blood than any other part, a view that would appear to receive some support from the fact that it is in this region that we most commonly meet with transverse softening, presumably due to vascular thrombosis and unfortunately and erroneously designated transverse "myelitis." On searching for anatomical evidence, however, in support of the view that the mid-thoracic region of the spinal cord is least well supplied with blood, we can find little to justify the

assumption, most of the evidence from this standpoint indicating rather that it is the lowest part of the thoracic cord and the lumbo-sacral region that is least well supplied with blood, both because this part of the cord is farthest from the origin of the anterior and posterior spinal arteries which are derived from the vertebrals in their course within the cranial cavity, and because the reinforcing arteries which reach the spinal cord by way of the nerve-roots have both a longer and a more vertical course from below up to this part of the cord, in addition to which of all the reinforcing arteries these are farthest away from the heart. Some observations conducted by Dr. Carrington, and referred to by the late Dr. Moxon in one of his suggestive Croonian Lectures (*Lancet*, 1881, i., p. 530), are worthy of attention in this connection. Injections were made into the femoral arteries in seven dead bodies, and in spite of its being *a priori* more probable that the vessels at the lower end of the spinal cord would be better injected than those at the upper end, the reverse obtained. In all the subjects the spinal arteries filled from above down, the injection either ceasing at the lower end of the cord or above that part, and while it was obviously reinforced by vessels which entered along the nerves, in no case were the reinforcing vessels of the nerves of the cauda equina found injected.

Much as all this bears against the possibility that the part of the cord most affected in the combined degenerations is that least well supplied with blood, it has to be remembered that it is not in the region of supply of either the anterior or posterior spinal arteries, or of the reinforcing arteries that enter the spinal cord by the nerve-roots that the degenerations occur, but that the degeneration is in the area of supply of the pial vessels.

We have next to consider the view that the spinal cord affection in the sub-acute combined degenerations is the result of myelitis. The objection which has been advanced against considering the degenerations as the result of hæmorrhages, to the effect that parts of certain tracts should be affected above such lesions and should escape below, while others should be affected below and escape above, is equally

applicable in the case of myelitis. Then, again, although we see all stages, including what appears to be the earliest of the changes in the spinal cord, we never meet with a round cell infiltration of the tissues so characteristic of changes of inflammatory origin.

The view that attributes the changes in the white columns of the cord to a primary affection of the gray matter appears to us to be erroneous in that in no small proportion of the total number of recorded cases, including all those of our present series, the gray matter has been found intact, while in a large number of cases in which changes have been found in the gray matter they have been slight and insignificant compared to the degeneration of the white matter, so that the latter could not possibly depend on the former changes. Moreover, there is a wonderful symmetry in the affection of the white matter, while changes in the gray matter when present are, as a rule, irregularly distributed. A further argument against this view is to be found in the fact that the parts of the white matter which chiefly escape are largely those the fibres of which are of endogenous origin.

There only remains for our consideration the view that a toxic agent is jointly responsible for the changes in the spinal cord and for the anæmia in those cases in which this symptom exists; and to this view we strongly incline. Although no poison has been determined in these cases, both the clinical picture and the morbid changes suggest that some toxin is responsible for the production of the disease. This toxic body (whatever may be its chemical nature) may reasonably be supposed to produce a parenchymatous degeneration by its action on the nerve elements of the spinal cord. Such a theory accords best with the changes found and with their distribution. The most reasonable explanation that can be offered as to why some parts of the cord are affected and others are not is that all parts of the central nervous system are not equally prone to be deleteriously affected by one and the same toxic agent, and that while certain parts are exceedingly easily damaged by one poison, others have a peculiar power of resistance to

the action of such a toxin, while it may be that these very parts are much less able to resist the action of some other toxin which may have little or no effect on the parts so susceptible to a poison having different properties.

Appendix of Clinical Cases and Pathological Results.

Case 1.—M. M., a stevedore, aged 27 years, was admitted into the National Hospital under the care of Dr. Bastian on October 27, 1897, complaining of numbness and loss of power in the legs and dysuria. He had always had the best of health previous to this illness. He denied venereal disease, and no fact was elicited suggesting that he had had syphilis. He had never taken excess of alcohol. He had suffered from a winter cough for many years.

Five months before admission he began to notice that his legs were numb and stiff, that he dragged his feet in walking, and caught his toes in the ground. A tight feeling round the lower chest troubled him greatly at times. A few weeks later he became unsteady when walking in the dark, and fell into his basin on several occasions when washing himself. He was treated at the London Hospital, where his condition was described as one of spastic paraplegia with ataxy and much anæsthesia of the legs. For three months before admission he had been losing his memory, and had become dull mentally.

Ten days before admission he became unable to stand or walk, and for the first time in his illness became unable to hold his urine. The legs which had been stiff till this time became quite flaccid. He had never had any shooting pains or "crises."

When admitted he was a powerfully built, ruddy faced man He was not anæmic. Mental state dull and drowsy. Memory bad. Special senses normal. Pupils equal and reacted normally. Divergent strabismus due to weakness of the right internal rectus; otherwise the cranial nerves were normal. Erectores spinæ and respiratory muscles normal. Great weakness of the lower half of the abdominal muscles, the umbilicus shifting upwards an inch on the attempt to sit up. All the movements of the upper extremities were very weak and were accompanied by tremulous incoordinate movements. The intrinsic hand muscles were wasted, and he could not approximate the thumb and little finger of either hand. There was marked hypotonia of the upper extremities. The electrical reactions of the muscles were normal.

Table of all the Physical Signs and Symptoms that have occurred in the Cases 1-9.

	First Stage.	Second Stage.	Third Stage.
Mental symptoms	—	—	Puerility; Delusions; Mania; Coma
Convulsions	—	rare	occasionally present
Speech and articulation...	—	—	—
Special senses	—	—	—
Cranial nerves	—	sometimes affected	—
Nystagmoid movements...	—	present	present
Pupils	equal and react	equal and react	equal and react
Palsy of trunk muscles	—	spastic palsy	flaccid palsy
Palsy of diaphragm	—	—	sometimes present
Upper extremities :—			
Paralysis	? slight	slight or marked	spastic or flaccid
Wasting	—	sometimes present	marked
Ataxy	present	marked	severe
Lower extremities :—			
Paralysis	slight spastic	severe spastic	complete flaccid
Wasting	—	sometimes present	severe
Ataxy	present	severe	extreme
Subjective sensations	present	present	present
Shooting pains	—	present	present
Girdle sensation	—	present	often present
Pain beneath costal margin	—	—	present
Herpes	—	present	present
Anæsthesia	—	partial loss	complete loss
Sphincters...	—	usually normal	incontinence
Superficial reflex excitability	+	+ +	+ +
Plantar reflexes	? extensor	extensor	extensor
Deep reflexes	increased	increased	lost
Pyrexia	present	present	present
Anæmia	present	present	present
Hæmorrhages	—	—	present

All movements of the lower extremities were performed feebly. The muscles were hypotonic, but were not wasted, and the electrical reactions were normal. When supported on either side he could just stand. The attempt to walk produced the most wildly incoordinate movements. There was complete loss of sensibility to all forms below the ninth dorsal root level and impairment to all forms as high as the fourth dorsal root level, and over both hands and the ulnar border of the left forearm. There was a marked girdle sensation immediately below the ensiform cartilage, and he complained of a constant heavy pain in the hepatic region. Reflex incontinence of urine with a considerable amount of residual urine. Severe cystitis. Cranium and spine normal.

Reflexes.—Wrist and elbow-jerks absent; knee-jerks only just obtained with double reinforcement; no foot clonus. Superficial reflex excitability of the lower limbs much increased. The plantar reflexes showed the extensor response. Some chronic bronchitis and emphysema. Temperature 101° F. No palpable enlargement of the spleen. The other organs were examined and found healthy.

A few days after admission the knee-jerks were lost and were never again obtained. The legs rapidly became completely paralysed. The muscles of the legs, forearms, and hands wasted rapidly, and their faradic excitability was lost early. Severe œdema of the legs and trunk appeared and lasted about a month, subsequently disappearing. He was twice seized with an attack of fine clonic spasm in all four extremities, without loss of consciousness. The anæsthesia became absolute everywhere below the sixth cervical root level. He became generally much emaciated, and died of asthenia on June 8, 1898. The blood examined two months before death showed hæmoglobin 25 per cent., R.B.C.'s 1,500,000 per cm. No nucleated red cells present.

Duration of illness—fifteen months; stage of slight ataxic paraplegia with anæsthesia—five months; stage of severe paraplegia with + knee-jerks—one month; stage of flaccid paralysis with absent knee-jerks, wasting, loss of faradic excitability, and œdema—nine months.

Post-mortem Examination.

The body was extremely wasted, the wasting being most marked about the lower extremities, which were fixed in a position of partial flexion at the hips and knee-joints. There

were several bedsores, both healed and open. There was an abscess in the left groin. Brain and membranes were normal. Spinal cord in external appearance was natural, but on section showed distinct sclerosis of the posterior and lateral columns. Heart and pericardium were normal. Lungs showed some patchy pneumonia. Liver was natural. Spleen was enlarged and friable. Kidneys were both enlarged, and showed a condition of pyonephrosis. Bladder showed evidence of chronic cystitis.

In sections prepared by the Weigert-Pal method all that was obviously wrong with the medulla above the level of the posterior column nuclei was degeneration in both lateral regions in the area occupied by the ventral cerebellar tract. More caudally there was, in addition to the degeneration in this situation, marked degeneration of the fibres of the posterior column nuclei and of the restiform body to a much slighter extent. Nothing obviously abnormal could be determined in the pyramids. In the upper cervical region there was complete degeneration of the posterior columns, the parts bounding the gray matter alone escaping. There was also marginal degeneration affecting the direct cerebellar and posterior part of the afferent antero-lateral tract, encroaching slightly on the crossed pyramidal tracts. The ventral part of the cord was preserved, with the exception of a very slight symmetrical degeneration in a very limited area in the efferent antero-lateral tract area. Lower in the cervical region some more of the postero-external column was preserved, the degeneration being on the whole less intense in this tract than in the postero-internal. There was in addition marginal degeneration, which affected the whole of the periphery of the remaining parts of the cord, including the direct pyramidal down to the anterior commissure. The crossed pyramidal tracts were considerably encroached upon, while the degeneration was rather less marked in the position of the efferent antero-lateral tracts than elsewhere in the affected parts. The same topographical distribution of the degeneration obtained in the thoracic region, though the extent of the area affected was greater; a smaller unaffected boundary separated the gray matter from the degenerated parts in the lateral and ventral regions of the cord, so that the crossed pyramidal tracts, for instance, were wholly involved while the lateral limiting layer escaped. In the lumbar cord the degeneration was less extensive in distribution; a considerable area in the antero-lateral region escaped, and there was no marginal degeneration at this point. In the posterior columns the fibres of the efferent septo-marginal tracts were seen to be unaffected. In the

lower lumbar and sacral regions the ventral portion of the cord was quite normal, the degeneration being limited to the crossed pyramidal tracts.

Sections prepared by the Marchi method confirmed what was shown by the Weigert-Pal method, and added the following information:—In the medulla, scattered recently degenerate fibres existed in both pyramids, and the areas of degeneration were more extensive than would be supposed from a study of the sections prepared by the other method alone. The same applies to the cord, for recently degenerate fibres were seen in areas which otherwise appeared normal. This method made it clear that in the affected parts three zones existed—(1) of advanced change, in which there was thick-set sclerosis, and little if any recent degeneration; (2) in which the bulk of the fibres was normal, but recently degenerate fibres were scattered throughout them; (3) an intermediate zone, in which the marked feature was the large clear spaces from which the products of degeneration had escaped. Thickened septa separated these spaces and scattered recently degenerate fibres, fewer than in the better preserved parts and more than in the sclerosed parts, lay among them.

The Nissl method revealed no abnormality in the cells of the gray matter of the cord, nor in those of the posterior root ganglia, nor could any change be determined in these parts by other methods of staining.

The nerve to the vastus internus muscle showed very considerable degeneration both by the Marchi and Weigert-Pal methods; by the Strœbe method many normal axis-cylinders could be seen, but it was noted that the medullated sheath of the nerve also tended to take the blue stain in an irregular manner, and a similar appearance was seen in the nerves of dogs in whom recent degeneration had been experimentally induced.

Muscles.—In the vastus internus there was extreme atrophy of the muscle-fibres, with a corresponding increase in the interstitial tissue between the fibres (plate v., fig. 1). There was also a considerable amount of fat within the individual muscle-fibres, and the transverse striation had disappeared from almost all, except a few of moderate size; but it is extraordinary to note how many apparently healthy well-medullated nerve-fibres lie in an area of muscle which is absolutely degenerate. Some of the atrophied muscle-fibres measured only ·004 mm., and even the largest measured only ·036 mm. The finer intermuscular nerve-fibres showed degeneration.

This case was examined also especially with regard to the muscle-spindle; it was found that the spindle, not only when teased out but also on transverse section, appeared normal, except for the fact that the nerves did not in every case stain well; the striation of the muscle-fibres within the spindle was well preserved, and apart from some fat within the fibres, they were normal. When stained by the Weigert-Pal method the nerve-bundles passing to the spindle stained badly, and comparatively few fibres were seen within the spindle; when, however, we consider the advanced degeneration of the muscle, the condition of the spindle was well preserved, although the nerve supplying it would seem to have undergone considerable degeneration.

Case 2.—J. S., a police constable, aged 36 years, was admitted into the National Hospital, under the care of Dr. Ferrier, on January 4, 1899, complaining of numbness and loss of power in all four limbs and loss of control over the sphincters.

His family history was unimportant. He had suffered with rheumatic fever and typhoid fever in childhood. He denied venereal disease. He had never indulged in excess of alcohol. He had always enjoyed good health, but had been much exposed to the weather.

The history of the illness was as follows:—On September 14, 1898, while at drill, he suddenly felt faint, and on reaching home vomited and had severe headache, which lasted three days. At the end of this time, on getting out of bed one morning, his ankles gave way under him, and from this time he suffered with a dull heavy pain in the loins and with a tight feeling round the stomach. The legs became numb and stiff, and he dragged them in walking. He was very ill generally, and frequently vomited.

In November, 1898, he rapidly lost power of standing, and suffered with severe shooting pains in the legs.

A month later the legs became completely flaccid, and he lost control over the sphincters. He suffered greatly with dyspnœa at this time.

When admitted he was a well-built healthy-looking man, with a flushed face and a distressed expression. He lay in bed breathing rapidly, and was unable to sit, stand, or walk. There was much soft œdema of the legs and trunk, and a large superficial sacral bedsore. The temperature ranged between 99° F. and 101° F.

His mental state was intelligent. He was delirious at night. The special senses, optic discs, and cranial nerves were normal. The pupils were equal and reacted normally.

The abdominal muscles, lower part of the erectores spinæ, and diaphragm were very weak, breathing being almost entirely thoracic.

The upper extremities were weak, but all movements could be performed against some resistance; no rigidity nor wasting. There was extreme incoordination and tabetic athetosis in both upper limbs.

The lower extremities were completely flaccid, and hypotonus was extreme. He could just move all the joints of the legs, but not against the least resistance. All the muscles of the limbs responded normally to both faradism and galvanism.

He complained of an intense heavy pain in the left hypochondriac region and of a broad girdle-sensation between the umbilicus and the ensiform process. Severe shooting pains in the legs. There was marked loss of sensibility to all forms below the twelfth dorsal root level, and generally ten seconds' delay in the perception of severe painful stimuli. There was complete loss of sense of passive movement in arms and legs. There was complete incontinence of sphincters, and there was cystitis.

Reflexes.—Wrist, elbow and knee-jerks absent; no foot clonus. Superficial reflex excitability of the lower limbs greatly increased. Plantar reflexes showed extensor responses.

Heart and lungs normal. Spleen not felt. No anæmia.

After admission the lower extremities rapidly became completely paralysed; the muscles wasted and lost their faradic excitability. The same event happened somewhat later in the hands and forearms. The diaphragm and lower intercostals became paralysed, and respiration became much embarrassed.

The anæsthesia gradually became complete, first over the sacral root areas and then step by step upwards till it reached the upper limit of the fourth dorsal root area.

The muscular wasting increased, and the galvanic excitability became much reduced. The knee-jerks were always absent. The superficial reflex excitability of the legs remained excessive. The extensor responses remained marked.

The patient died of respiratory failure twenty days after admission. Blood count two days before death: hæmoglobin 90 per cent.; red corpuscles 4,500,000 per c.mm.; no nucleated red cells.

Duration of symptoms—four months; stage of slight ataxic paraplegia—nine weeks; stage of severe palsy with rigidity—four weeks; stage of flaccidity, wasting, loss of faradic excitability, absent knee-jerks, and complete anæsthesia—three weeks.

Post-mortem Examination.

The body was poorly nourished, the wasting of the lower extremities being out of all proportion to that of the rest of the body; a bedsore was present over the sacrum. There was some patchy consolidation of the lungs. The spleen was enlarged, but the other organs of the body appeared healthy. The spinal cord, so far as its external surface was concerned, appeared to be healthy, but on section degeneration in the posterior and lateral columns was apparent.

Microscopical Examination.

Cortex.—The cells of the cerebral cortex and the tangential fibres appeared normal; no degeneration could be seen by the Marchi method. The cerebellum and pons appeared perfectly normal.

Medulla.—The upper portion of the medulla appeared perfectly normal both by the Marchi and Weigert-Pal methods. At the level of the posterior column nuclei there was by the Marchi method degeneration in the funiculus gracilis and cuneatus and in the direct cerebellar tracts, but only a few degenerate fibres could be seen in the pyramids. By the Weigert-Pal method degeneration could only be seen in the funiculus gracilis.

Spinal cord.—The brunt of the disease had fallen on the mid-dorsal region, and had affected the posterior columns and the region occupied by the crossed pyramidal tracts more than the ventral region of the cord, although there were numerous patches of degeneration even in this area. In the cervical region the degeneration was limited to the posterior columns, the crossed pyramidal and the direct cerebellar tracts, and had left the ventral portion of the cord even less affected than in the dorsal region. The degeneration was much more scattered and patchy than in some of the other cases, and did not affect the whole periphery of the cord in the mid-dorsal region to so marked an extent.

By the Marchi method there was considerable degeneration both in the regions above described and also around them. There was considerable vacuolation in the mid-dorsal region of the cord, but the recent degeneration, as shown by the Marchi method, was most marked in the long tracts of the cord.

By the Nissl method the cells of the anterior horn, although somewhat pigmented, appeared perfectly normal; the cells of Clarke's column also were normal.

By van Gieson's method there was considerable thickening of the walls of the vessels in those areas of the cord where the degeneration was most marked, while in the region of the cord where there was no change there was no engorgement or thickening of the vessels. In the gray matter of the cord in the mid-dorsal region the vessels appeared full and engorged, although there was no actual exudation round them. The posterior nerve-roots appeared normal. The cells of the posterior root ganglia also appeared normal but were considerably pigmented. The Marchi method showed no degeneration.

Peripheral nerves.—By the Marchi method there was some degeneration in the left sciatic and left anterior crural nerves, and more in the left than the right phrenic nerve. In the corresponding nerves of the right side the degeneration was equally marked, and by the Weigert-Pal method some atrophy of the nerve fibres could be seen.

Muscles.—The fibres of the left vastus internus muscle were fairly uniform in size, but were below the average of the normal muscle, measuring about ·04 mm. The transverse striation was well marked and there was no fatty change. The right vastus internus was in the same condition, the fibres measuring ·04 mm. in diameter. The striation was well marked and there was no fatty change.

Case 3.—S. D., a married woman aged 48 years, was admitted into the National Hospital under the care of Dr. Bastian on January 20, 1899, complaining of stiffness and numbness of the legs.

Three years before admission she began to suffer with a tumour in the left loin, and two years later the left kidney was excised for pyonephrosis. She recovered completely from this operation. With this exception her health had always been good. Several facts were elicited suggesting that she had had syphilis. She had not taken excess of alcohol.

Her illness began in September, 1898, when she first noticed weakness and stiffness and numbness in the legs. Shortly afterwards she fell downstairs, and subsequently had great difficulty in walking and had slight incontinence of urine. The legs gradually got worse and she became very pale. A girdle sensation appeared just above the umbilicus.

When admitted she was a very anæmic, sallow-complexioned woman. She was well nourished. Her mental state was reduced and her memory was poor. Speech, articulation, special senses,

optic discs and cranial nerves were normal. The pupils were equal and reacted normally. The abdominal muscles below the umbilicus were very weak, and the umbilicus shifted upwards an inch in the attempt to sit up. All movements of the upper extremities were performed strongly. There was slight ataxy of the hands. All movements of the lower extremities were performed very feebly and were very ataxic. The legs were slightly rigid at all joints. There was no wasting. There was marked blunting of sensibility to all forms below the ninth dorsal root area. Complete loss of sense of passive position in the legs. She complained of shooting pains in the legs and of a girdle sensation just above the umbilicus. Slight incontinence of urine.

Reflexes.—Wrist, elbow, and jaw-jerks were brisk. Knee-jerks exaggerated. Double foot clonus. Superficial reflex excitability of the lower limbs much increased. Plantar reflexes were extensor responses.

Urine normal. Temperature ranged between 98° F. and 102·5° F. The spleen could not be felt. There was a loud hæmic murmur to be heard in the neck. No hæmorrhages were found. Blood count: Hæmoglobin 20 per cent., R.B.C.'s 1,800,000 per cm. Red cells all sizes and irregular in shape. No nucleated forms. Some Eichhorst's cells seen. There was a marked lymphocyte leucocytosis and no hyaline cells were seen.

A week after admission the legs became quite flaccid, the knee-jerks were lost, the anæsthesia and incontinence became complete, the muscles began to waste and to lose their faradic excitability, and œdema of the legs and trunk appeared, the extensor plantar reflexes remaining.

Under treatment with iron and arsenic the anæmia improved considerably, the hæmoglobin reaching as high as 50 per cent., but it gradually fell again to 20 per cent. The œdema disappeared. The lower extremities became extremely wasted, the muscles entirely losing their excitability to faradism; the diaphragm became paralysed. Bedsores developed. The patient died suddenly of syncope five weeks after admission.

Duration of illness—six months; stage of ataxic spastic paraplegia—four months; stage of flaccid paraplegia—two months.

Post-mortem Examination.

The body was fat, the limbs were flaccid. The brain showed some shrinking of the convolutions on the right side about the upper part of the ascending parietal convolution, but otherwise

was normal. The spinal cord was somewhat shrunken and firmer than normal, and on section showed changes in the posterior and lateral columns. There was some fluid in both pluræ, and the bases of both lungs were considerably collapsed. The heart appeared normal. The liver was enlarged and weighed 60 ozs. Spleen was large and soft and weighed 12 ozs. The left kidney was absent (removed by operation). The right weighed 8 ozs. and was covered by small raised nodules (septic infarcts). The bladder showed cystitis. The muscles of the lower extremity were pale, flabby, and very watery; the biceps cubitis was of normal appearance.

Cortex.—Microscopical examination of the cerebral cortex both with regard to the cells, the medullated fibres, and the tangential fibres, showed no change in these structures.

Cerebellum and pons.—Both these appeared normal by the Weigert-Pal and Nissl methods, but by the Marchi method degenerate fibres could be seen in the ventral cerebellar tract and in the velum, but no other degeneration could be seen at this level.

Upper level of the medulla.—This region appeared normal by the Weigert-Pal method, but by the Marchi method degeneration could be seen in the restiform bodies and in the ventral cerebellar tracts, and there was also scattered degeneration throughout both pyramids. In the medulla the degeneration first became marked at the level of the posterior column nuclei by the Weigert-Pal method and was present in the pyramids, in the direct cerebellar tract, and in the funiculus gracilis and cuneatus. The same section stained by Marchi shows very considerable degeneration of a recent character in the direct cerebellar tracts and older change leading to vacuolation in the pyramids.

Spinal cord.—By the Weigert-Pal method the degeneration was most marked in the dorsal region of the cord, where it affected almost the whole of the white matter except a small zone immediately surrounding the gray matter. The sclerosis was rather more marked in the crossed pyramidal tracts than in the other parts of the cord in this region. In the cervical region of the cord the degeneration was less extensive and was more patchy in distribution—for instance, there were numerous irregular patches of sclerosis in the region of the direct pyramidal tract, while the portions of the cord external to this were less affected. In the upper cervical region the destruction wa smost marked in the posterior columns and in the cerebellar tracts. Passing then to the lower dorsal and

lumbar region, it was found that there was some affection of the posterior columns down to the lower lumbar region, but the sacral was quite free. There was degeneration corresponding to the crossed pyramidal tracts in the lower dorsal, lumbar and sacral regions, and in the latter region it was the only degeneration present. By the Marchi method all the features as above described were present, but it was very striking how little recent degeneration, as evidenced by the presence of fat granules, was present, while the vacuolation and sclerosis of the cord were marked features, and it was only in the areas that appeared normal by the Weigert-Pal method that any number of recently degenerated fibres could be seen. The gray matter of the cord and the cells of the anterior horn and the cells of Clarke's column appeared normal. It could not be positively asserted that there was no change, nor that there was no diminution in the number of the cells of the anterior horns, but it could be asserted that there were numerous perfectly normal cells in the anterior horns in every region of the cord.

Sections stained by van Gieson's method showed that there was no inflammatory condition in the gray matter. In the areas in which the sclerosis of the cord was most marked the vessels were full and engorged and their walls were thickened, but there was no evidence of thrombosis, and in the normal regions of the cord the vessels were neither dilated nor thickened. There was no change in the pia-arachnoid membranes of the cord.

Anterior nerve-roots appeared normal both by the Weigert-Pal and by the Marchi method. The posterior nerve-roots also appeared normal by both methods.

Posterior root ganglia.—No change could be found in these either by the Nissl or Marchi methods. The cells were, however, extensively pigmented.

Peripheral nerves.—No change could be found in any of the following peripheral nerves which were examined by the Marchi and Weigert-Pal methods—right and left sciatic, median, anterior crural, and phrenics.

Muscles.—Right rectus femoris: The fibres of this muscle varied very greatly in size, the largest measuring only ·04 mm. in diameter and the average less than ·02 mm. The striation was well preserved. Left vastus internus: The description given above of the right rectus femoris will apply to this muscle. There was no fatty change within the muscle fibre. Right biceps: The fibres of this muscle were much less atrophied than those above described and were far more uniform in size.

Case 4.—M. D., a married woman, aged 39 years, was admitted into the National Hospital, under the care of Dr. Bastian, on August 16, 1899, complaining of general loss of strength and anæmia of two years' duration and of loss of power and feeling in the legs of six weeks' duration. Until this illness her health had always been good. No facts were elicited suggesting that she had had syphilis. She had indulged freely in alcohol. She lived in the same street as the patient S. D., in Case 3 just described.

Two years before admission, without any assignable cause, she lost her strength, and became very pale and breathless. Her medical attendant found that she was suffering from severe anæmia and irregular pyrexia. She remained confined to bed for six months, and then slowly got better, but never regained her original strength.

Three months before admission she first noticed numbness, weakness, and unsteadiness in the legs. These symptoms increased, but she was able to get about and to do her housework till a week before admission. During this time she had severe shooting-pains in the legs and had a constant heavy pain beneath the left costal margin, and a girdle sensation just below the ensiform process.

A week before admission she became unable to stand, the legs and hands became very numb; she had incontinence of urine, œdema of the legs, and several fainting attacks. The legs at this time became very stiff.

When admitted she was a well-nourished woman. The skin was very pale and sallow. Her mental state was one of extreme exhaustion, and she was delirious at night. Temperature from 98° F. to 101° F. Speech, articulation, special senses, optic discs, and cranial nerves were normal. The pupils were equal, and reacted normally. The abdominal muscles and lower part of the erectores spinæ were very weak. She could not sit up in bed or maintain the sitting posture when raised. The movements of the upper extremities were feeble, and there was marked incoordination. There was some fine tremor of the fingers. The lower extremities were flaccid, and all movements were extremely feeble; great incoordination and marked hypotonia; some general wasting. All the muscles of the lower extremities showed great diminution of excitability to faradism and galvanism; A. C. C. > K. C. C. She complained of occasional shooting-pains in the legs and of a severe dull pain beneath the left costal margin. There was a tight girdle sensation at the level of the ensiform process.

There was distinct diminution of sensibility to all forms, evenly distributed below the fourth dorsal root level and over the eighth cervical and first dorsal root areas. There was complete loss of sense of passive position in the lower extremities, and marked loss in the hands. There was reflex incontinence of both sphincters.

Reflexes.—Wrist, elbow, and knee-jerks absent. The plantar reflexes showed the extensor response. The superficial reflex excitability of the lower limbs was much exaggerated.

Heart.—There was a soft apical systolic murmur and a loud venous hum in the neck. The pulse was regular and of low tension. Blood count, August 20: Hæmoglobin, 56 per cent.; red blood cells, 4,000,000 per cm.; no poikilocystosis; no nucleated red cells; a few Eichhorst's cells; white cells normal. There were no hæmorrhages. She was treated with arsenic, strychnine, and iron.

On August 21 she had a syncopal attack, and in the course of the next half-hour the right upper extremity became very œdematous as high as midway between the elbow and shoulder. Four hours later the œdema of the arm had completely disappeared.

She left the hospital against advice on August 24, but was readmitted on September 16 profoundly anæmic and with a large sacral bedsore.

Blood count on October 2: Hæmoglobin, under 20 per cent.; red blood cells, 800,000 per cm.; marked poikilocystosis; no nucleated red blood cells; no Eichhorst's cells; ratio of white cells to red, 1 to 40. There was marked increase in the number of lymphocytes. No coarse oxyphile or hyaline cells were seen in stained specimens.

There was then marked œdema of the lower extremities and of the hands. The upper extremities were almost completely paralysed, and the muscles only reacted to strong faradic stimulation. There was complete flaccid palsy, with great wasting, loss of faradic excitability, and polar change in the muscles of the lower extremities. There was almost complete anæsthesia to all forms below the seventh cervical root area, and absolute anæsthesia below the fourth dorsal root level. There was complete incontinence of both sphincters. The deep reflexes were absent; the plantar reflexes were still extensor responses. She was constantly delirious; the temperature remained above normal; and she died of respiratory failure on October 19.

Duration of illness: Anæmia—two years; nervous symptoms—five months; stage of spastic paraplegia—ten weeks; stage of flaccid paraplegia—ten weeks.

Post-mortem Examination.

Body well nourished and fat; the limbs were flaccid. There was a bedsore over the sacrum. The brain was normal; the spinal cord appeared normal on its external surface, but on section showed degeneration of the lateral and posterior columns. The heart was flabby and appeared fatty, but the valves were normal. The lungs were very œdematous. The liver was large, weighed 67 ozs., and was friable and fatty. On testing it for free iron a reaction developed which was inconclusive, but subsequent microscopical examination showed that none was present. The spleen weighed 16 ozs., and was diffluent. The kidneys were slightly granular, but were otherwise normal. The bladder appeared fairly normal. The bone marrow of the femur was of a dark red colour, almost diffluent, and very like the spleen in consistency. The muscles were pale, flabby, and very watery.

Microscopical Examination.

Cortex cerebri.—This was normal both as regards the cells, medullated fibres, tangential fibres, and the Marchi method revealed no degeneration. Cerebellum and pons appeared normal.

Medulla.—The upper portion of the medulla appeared normal by the Weigert-Pal method. By the Marchi method, however, degenerated fibres could be seen in both direct cerebellar tracts and in the restiform bodies. At the level of the decussation there was considerable degeneration in both cerebellar tracts, in both the funiculus gracilis and cuneatus, and in the pyramids, as shown both by the Marchi and Weigert-Pal methods.

Spinal cord.—By the Weigert-Pal method there was degeneration of the posterior columns from the lumbar to the cervical region; the destruction was most marked in the dorsal region, somewhat less in the cervical, still less in the lumbar, while the sacral region escaped altogether. The areas of degeneration were rather patchy, but in the cervical region the degeneration was more marked in the column of Goll than in the column of Burdach. There was degeneration in both lateral columns of the cord especially marked in the peripheral portions of the cord in dorsal region. The degeneration in the pyramids could be traced from the cervical to the sacral region, but below the mid-dorsal region it assumed the character of a descending degeneration. The direct cerebellar tract was degenerated, and could be traced up to the restiform body. The fibres in immediate relation with the gray matter appeared fairly normal. The recent degeneration

as shown by the Marchi method was very slight, and the areas which showed most fatty granules were those belonging to the long tracts of the cord. The cells of the anterior horn were somewhat pigmented, but otherwise appeared normal; and the cells of Clarke's columns also were normal.

Vessels.—In the regions of the cord where the sclerosis was most marked there was thickening of the walls of the vessels which affected chiefly the middle coat. In the normal portions of the cord the vessels appeared normal.

Posterior roots.—These appeared perfectly normal.

Posterior root ganglia.—The cells of these ganglia were well formed and appeared normal, though there was rather a large amount of pigment present.

Peripheral nerves.—The following nerves were examined and appeared normal:—The right anterior crural and the branch to the right vastus internus muscle, the nerve to the left rectus femoris, and the left sciatic.

Muscles.—The muscle fibres of the right vastus internus were considerably atrophied, the average diameter being somewhat under ·04 mm.; there was no fatty change within the muscle fibres, and the striation was well marked. The muscle fibres of the left rectus femoris were of irregular size, and averaged about ·032 mm. in diameter, and the striation was well marked.

Liver.—No free iron could be detected in the liver. There was a good deal of fat, but not more than is often found in the livers of persons dying of wasting diseases.

Kidneys.—These appeared normal.

Case 5.—E. F., a married woman aged 49 years, was admitted into the National Hospital under the care of Dr. Hughlings Jackson on December 23, 1898, complaining of loss of power in both legs, sphincter trouble and bedsores.

The family history was unimportant. Previous to this illness her health had been good; there was no history of syphilis and she had always been most abstemious as regards alcohol.

The history of the illness was as follows:—A year before admission the legs became numb and weak and were easily tired. Soon after she dragged the legs in walking and was unsteady when standing, and had occasional diplopia. For ten months she remained able to do her work, but at the end of this time she rapidly became quite unable to stand, and had severe shooting pains in the legs.

A month before admission the legs, which up to this time had

been stiff, became quite flaccid, she completely lost control of the sphincters and developed œdema of the legs and trunk, and a large bedsore made its appearance.

When admitted she was a well-nourished, healthy-looking woman. She was not in the least anæmic. She was quite unable to move the legs and trunk, she was completely incontinent, and there was a large sacral bedsore. She had severe cystitis, and the temperature was 102° F. By day she was mentally clear, but at night there was noisy restless delirium. Speech, articulation, special senses and optic discs were normal. The pupils were equal and reacted normally. There was marked weakness of both external recti. The abdominal muscles were completely paralysed below the umbilicus. The upper extremities were slightly tremulous, but were otherwise normal. There was complete flaccid palsy of the lower extremities. All the muscles were much wasted. None of the muscles of the lower extremities reacted to faradism and the reaction to galvanism was very feeble. There was absolute loss of sensibility to all forms below the first lumbar root level, and marked impairment to all forms as high as the tenth dorsal root level. There was complete loss of sense of passive position in the lower extremities and some impairment in the hands and fingers. There were some trophic changes in the skin of the feet. There was complete incontinence of both sphincters and severe hemorrhagic cystitis.

Reflexes.—The wrist and elbow-jerks were exaggerated. The knee-jerks were totally absent; there was no foot clonus, but two months before admission she had been seen by Dr. Tooth, and he had made a note that at that time the knee-jerks were exaggerated and that there was double foot clonus. There was much soft œdema of the legs and lower part of the trunk. The spleen was not palpably enlarged. There was no anæmia. The other organs were examined and found healthy. She died comatose thirteen days after admission.

Duration of symptoms—thirteen months; stage of slight ataxic paraplegia—ten months; stage of severe paraplegia—one month; stage of flaccid paraplegia, absent knee-jerks and œdema—six weeks.

Post-mortem Examination.

Body well nourished, excess of adipose tissue, bedsore over sacrum. All the organs of the body appeared normal except the spinal cord, which showed on section distinct changes in the posterior, antero-lateral and anterior columns.

Microscopical Examination.

Cerebral cortex appeared normal both as regards its cells and the tangential fibres, and no degeneration could be seen by the Marchi method. Cerebellum was normal.

Pons.—There were scattered degenerate fibres in both pyramids in the pons and in the superior cerebellar peduncles. By the Weigert-Pal method the pons appeared normal.

Medulla.—There were scattered degenerate fibres throughout both pyramids and both restiform bodies as seen by the Marchi method.

Lower level of the medulla.—Degeneration of both direct cerebellar tracts was most marked, there was scattered degeneration in both pyramids and also in the funiculus gracilis and funiculus cuneatus, but more marked in the former than in the latter. By the Weigert-Pal method some change could be seen in the direct cerebellar tracts and in the posterior columns, but the pyramids appeared normal.

Spinal cord.—By the Weigert-Pal method the degeneration was most marked in the dorsal region of the cord, affecting the posterior and crossed pyramidal tracts to the greatest extent, leaving the ventral portion less affected. In the cervical region the posterior columns were more affected than the lateral, while in the lumbar region the lateral columns were more affected than the posterior. The process in this case would seem to be much less destructive than in some of the other cases, there being more recent degeneration and more sclerosis, but less vacuolation; the distribution of the degeneration is, however, the same. By the Marchi method there was in the cervical region marked degeneration in the posterior columns, especially in Burdach; the columns of Goll were so sclerosed that they showed little recent degeneration. Degeneration was also present in the pyramidal and direct cerebellar tracts, and in a few fibres in the ventral columns of the cord, while in the lumbar region some degenerate fibres could also be seen in the posterior column and in the ventral region of the cord. In the sacral region there was degeneration in the crossed pyramidal tracts alone.

Van Gieson's method: The gray matter appeared normal. The vessels in the affected areas were thickened and engorged, but were not thrombosed; in the unaffected areas of the cord they appeared normal.

Nissl method: The cells of the cervical and dorsal region of the cord were possibly fewer in number than normal, but those remaining were well stained and appeared normal. The cells in

the lumbar region appeared perfectly normal. The cells were considerably pigmented.

Peripheral nerves.—The following peripheral nerves were examined and were found to be perfectly normal both by the Marchi and Weigert-Pal methods—the right and left sciatic, left anterior tibial, the nerves to the right and left vastus internus muscles, and the nerves to the right and left vastus externus muscles.

Muscles.—Right rectus femoris: The fibres of this muscle are somewhat atrophic, averaging about ·04mm. in diameter; they are well striated and show but slight fatty change within the fibres. Right vastus externus muscle: The fibres vary greatly in size, having a rounded instead of polygonal outline; there were several degenerate fibres scattered throughout the muscle, which showed black granules when stained by osmic acid; these fibres are not numerous, and are always of small size, ·02—·03mm. Right vastus internus muscle exhibited the same condition as the above two muscles. It is very noticeable, however, how few nerve-fibres there are in the muscle tissue when stained by Pal's method when compared to the normal. When, on the other hand, one compares the condition with that found in case No. 1, in which, in spite of the extreme atrophy of the muscle, the nerve-fibres are well preserved, one cannot but think that the absence of nerve-fibre in this portion of the muscle is a fortuitous condition.

Case 6.—Ruth M., aged 45 years, was admitted into the National Hospital under the care of Dr. Hughlings Jackson on June 30, 1897, complaining of paralysis of the legs and sphincter trouble. There was a history of epilepsy, cancer, and of phthisis in the family. She had been a strong, healthy woman, and she had probably had syphilis. She had been addicted to alcohol. A very incomplete history of the illness was obtained owing to the patient's mental state and the absence of any friends who were in a position to give a detailed history.

Her illness dated from six weeks before admission, when she began to complain of numbness of the hands and feet, stiffness of the legs, and difficulty in walking.

A fortnight later she became unable to stand, developed a girdle sensation and sphincter trouble. She had frequent fainting attacks, and several attacks of general convulsions, in which she lost consciousness and passed urine.

When admitted she was a poorly nourished woman, unable to stand or walk. There was some mental obfuscation. Speech,

special senses, optic discs, and cranial nerves were normal. The pupils were irregular, and there were anterior synechiæ in both eyes. The upper extremities showed some slight incoordination, but were otherwise normal. The respiratory muscles and erectores spinæ were normal; the lower half of the abdominal muscles were weak. Both lower limbs were rigidly extended and were completely paralysed. There was diminution of sensibility to all forms below the ninth dorsal root level, and a tight girdle sensation at this level. There was distension of the bladder with overflow.

Reflexes.—Wrist and elbow-jerks increased; knee-jerks exaggerated. Double foot clonus. Superficial reflex excitability increased in the legs. Plantar reflexes brisk. Marked anæmia. Blood not examined. Liver and spleen not palpably enlarged.

After admission the temperature remained above 101° F. She was constantly delirious. The legs became flaccid, the knee-jerks disappeared, and slight œdema of the lower extremities appeared. The anæsthesia became absolute, the sphincters completely incontinent, and she died much emaciated seven weeks after admission.

Duration of illness—fourteen weeks; stage of spasticity—eleven weeks; stage of flaccidity—three weeks.

Body much emaciated. Brain: the convolutions were somewhat shrunken and there was slight compensatory œdema, otherwise normal. Spinal cord was normal to external appearances, but on section showed sclerosis of the posterior and lateral columns. The heart was natural. The lungs were œdematous. Liver was large and firm, and there was evidence of old perihepatitis. The kidneys were normal.

Microscopical Examination.

Sections of the medulla and spinal cord showed by the Weigert-Pal method that at the level of the pyramidal decussation there was extensive degeneration of the fibres of the posterior column nuclei and of the lateral region of the medulla in the area occupied by the cerebellar tracts, in addition to which there were two small areas symmetrically placed in the antero-lateral region of the medulla. Moreover, a patchy degeneration was evident in the pyramidal fibres at the decussation. The upper cervical cord was the seat of complete degeneration of the posterior columns except the part bordering on the gray matter. There was extensive degeneration of the lateral columns, but the ventral portion

of the cord was preserved. In the lower cervical cord a similar condition was present but to a less marked degree, in the dorsal portion of the posterior external column, while the lateral column degeneration was more extensive, and there was here patchy degeneration in the region of the direct cerebellar tracts, though not confined to these. In the thoracic cord the posterior degeneration was as extensive as in the upper cervical region, and in the lateral areas of the cord more extensive than at the higher levels, as was also the degeneration of the direct pyramidal tracts, which obviously extended beyond the strict limits of these. The only parts of white matter preserved were those bordering on the gray. In the lower thoracic region some fibres in Goll's column were preserved, and there was less extensive degeneration in the ventral parts of the cord. In the lumbar region there was no degeneration in Goll's column, but some in Burdach, especially in the peripheral portion, while the whole of the ventral portion of the cord was preserved.

The Marchi method revealed scattered degenerated fibres in the pyramids, in the lateral region of the medulla in the parts occupied by the cerebellar tracts, and also in the restiform body, but not confined to the area normally occupied by these tracts. There were degenerate fibres in the posterior column nuclei. The condition found in the spinal cord confirmed the findings by the Weigert-Pal method. The great feature of the Marchi specimens was not so much the bringing into evidence of recently degenerated fibres, of which there are comparatively few, but the making evident of spaces by the falling out or absorption of the destroyed fibres. Fibres that still stain black are seen in the less affected parts, *e.g.*, in the white matter bordering on the gray. The parts of the cord most destroyed were the postero-lateral and ventral, the part between these two areas in the antero-lateral region being less affected. In the upper sacral region there was some falling out of the fibres in the neighbourhood of the ground bundles, but there were scarcely any black fibres. In the lower sacral region no change was found except a few black fibres on each side of the posterior median septum. No descending degeneration was evident, in spite of the lateral columns being extensively destroyed in the lumbar region of the cord.

Case 7.—S. W., aged 38 years, was admitted into the National Hospital, under the care of Dr. Bastian, on November 23, 1899, complaining of paralysis and numbness of the legs, swelling of the legs, and loss of control over the sphincters. There was a strong

family history of tubercular disease. He had been a strong healthy man. He had had syphilis when 22 years old, and had been a heavy beer drinker. A year before this illness commenced he suffered with inflammation of the bladder.

Three years before admission he caught a chill, and directly afterwards noticed that his feet felt numb and stiff. During the next two years the numbness gradually crept up the legs and invaded the trunk, and he was unsteady and dragged his legs in walking, but he kept at his work without much difficulty.

Six months before admission he suffered with severe shooting-pains in the legs. His legs became very stiff, and he became much more unsteady, could not walk in the dark, and fell into his basin when washing. At this time he was a patient at Charing Cross Hospital, where the presence of double foot clonus and increased knee-jerks was noticed.

He remained in this condition without the development of further symptoms till six weeks before admission, when in the course of a few hours he became unable to stand, and for the first time during his illness lost control of the sphincters; this loss remained complete. The loss of sensibility of the legs and trunk became much more severe; he became very pale in the face, and œdema of the legs appeared. He developed cystitis, and became delirious at night.

When admitted he was a pale, sallow-faced, sparely-nourished man. The skin had a waxy-yellow appearance. He lay on his back in bed, unable to move the legs or trunk. He was delirious at night, and his temperature was 102·5°. He had severe cystitis and much hæmorrhage from the bladder. His mental state was facile, and he had varied delusions. On two occasions he had an attack of general convulsions lasting ten minutes, during which time he was comatose. The special senses and cranial nerves were normal. The retinal fundi were yellow in colour, and there were a few small hæmorrhages. The pupils were small and equal; they reacted normally. The erectores spinæ and abdominal muscles did not contract on attempting to sit up or on the attempt to move the trunk. The lower intercostals moved badly in respiration; the diaphragm acted well. All movements of the upper extremities were performed feebly and with marked ataxy. The weakness was more marked in the periphery and the intrinsic muscles of the hands, and the ulnar flexors were markedly wasted. In these muscles faradic excitability was much diminished; to galvanism, K. C. C. > A. C. C. There was absolute paralysis of the lower extremities, with slight flexor and

adductor spasm. There was some rigidity at all joints, but the muscles hung loosely on the bones and were flabby. There was no wasting. There was some diminution to faradism below the knees. There was a severe girdle pain round the lower part of the chest and some shooting pains in the legs. There was complete analgesia to all forms of moderate stimuli from the upper limit of the first lumbar root distribution. Light touches and pricks were not felt below the fifth dorsal root level. There was complete loss of sense of passive position in the lower extremities and marked loss in the joints of fingers and hands. Absolute incontinence of both sphincters. Severe cystitis. Cranium and spine normal. Severe bedsore on left hip. The knee-jerks were exaggerated; no foot clonus; wrist and elbow-jerks brisk. The plantar reflexes were brisk extensor responses, and there was some dorsal retraction of the great toes. The reflex excitability of the lower extremities was greatly exaggerated. There was marked breathlessness on slight exertion; loud basic systolic murmur and *bruit de diable*. Pulse, very low tension. Blood count: Hæmoglobin, 30 per cent.; red blood cells, 1,600,000 per cm.; white blood cells; a marked lymphocyte leucocytosis; very few hyaline cells seen; all other normal forms seen; no poikilocytosis; no microblasts, normablasts, and no gigantoblasts; no Eichhorst's cells found. There was no palpable enlargement of the spleen or of the lymphatic glands. No œdema was present at the time of admission. No abnormality was found in the other organs.

During the first week after admission the clinical picture changed remarkably; the deep reflexes disappeared, and were never again obtained. The spastic condition of the lower limbs gave place to one of complete flaccidity. The muscles of the legs and hands wasted rapidly and lost their faradic excitability within a few days. The excitability to galvanism and to percussion were almost abolished. Much soft œdema of the legs and back appeared, and lasted about three weeks. A heavy constant pain was complained of in the left hypochrondriac region. The cystitis was soon cured with appropriate treatment, and the bedsore healed. Following a severe attack of pain in the left side, a cutaneous hæmorrhage, precisely limited to the area of distribution of the seventh left dorsal root, appeared with two smaller patches over the tenth and eleventh left dorsal root areas. Trophic changes in the skin, similar to those seen in neuritis, occurred in the four extremities. The wasting of the muscles was progressive, and the diaphragm became paralysed.

The plantar reflexes constantly were extensor responses, and the superficial reflex excitability of the lower limbs remained excessive.

Death occurred from exhaustion.

Post-mortem Examination.

The body was extremely thin and wasted, there was a sloughing bedsore over the sacrum, and the scar from an old hæmorrhage in the area corresponding to the seventh thoracic root of the left side. The skull and membranes of the brain were normal. The convolutions of the brain appeared normal, and the cranial nerves and the vessels were natural.

Spinal cord.—There was some purulent exudation on the outer surface of the dura mater in the lower part of the spinal canal arising from the bedsore over the sacrum. The external appearance of the cord was natural, there was no wasting, and the anterior and posterior roots appeared of normal size. There was no meningitis or thickening of the pia-arachnoid. On section the gray areas of degeneration were distinctly visible. The lungs were healthy except for some œdema at the bases. The heart was normal. The diaphragm was natural. The liver was slightly enlarged and gave no free iron reaction. The spleen was enlarged, soft and pulpy. The kidneys showed considerable pyelitis, and the infective infarcts were more numerous in the right than in the left. The bladder contained some purulent urine, and showed a condition of chronic cystitis. The bone marrow of the right femur was examined and appeared pale and of normal consistence. The muscles were wasted, but were not very pale nor œdematous. The right sciatic nerve was evidently very fatty. The posterior root ganglia appeared normal to the naked eye except the seventh left dorsal, and on making an incision into this, after it had been hardened in formalin it was found to contain a small cyst measuring about 3 mm. in diameter, and this contained a little clear fluid.

Microscopical Examination.

By the Weigert-Pal method the cortex appeared normal, the tangential fibres were well stained, the pons and upper levels of the medulla also appeared normal. In sections taken through the lower portion of the olive some change could be seen in the pyramidal tracts, and there was considerable vacuolation in this area; the direct cerebellar tract was similarly affected. In sections below the level of the posterior column nuclei degenera-

tion could be seen in the funiculus gracilis and funiculus cuneatus, the direct cerebellar tract, and in both pyramids. At the level of the decussation of the pyramids there was marked degeneration of the posterior columns, both internal and external, and also of the direct cerebellar tracts; both pyramids were also markedly affected. In the upper cervical region there was extensive sclerosis of the posterior columns, the direct cerebellar tract, and also very considerable affection of the pyramids, but though most marked in these is not limited to them. The nearer the sections examined to the mid-dorsal region the more extensive was the sclerosis, and it was no longer limited to the tracts above-mentioned but affected the whole of the periphery of the cord, leaving the gray matter and a small band of medullated fibres that immediately surrounded it alone normal. At the level of the twelfth dorsal the posterior columns were still markedly affected, but there was less degeneration in the ventral portion of the antero-lateral tracts, the degeneration of the pyramids was still marked. In the lumbar region the posterior columns still showed considerable degeneration, and there was degeneration both in the region of the direct and crossed pyramidal tracts, although it was not strictly limited to the tracts.

Marchi method.—In the cortex there were a few degenerate fibres in the white matter, and these could be traced down into the crura, being rather more numerous on the one side than the other. In the pons degenerate fibres could be seen in both pyramids and in the ventral cerebellar tract, and in addition to this there was a small area of softening with degenerate fibres just ventral to the posterior longitudinal bundle. In sections taken through the upper part of the medulla, scattered degenerate fibres could be seen in the pyramidal tracts, and in the direct cerebellar tracts these were more numerous and could be seen passing into the restiform bodies. Scattered degenerate fibres could also be seen in the region of the posterior column nuclei. In sections taken through the medulla at a lower level, scattered degenerate fibres could be seen in both pyramids, the direct cerebellar tract, and in the funiculus cuneatus, the degeneration being more marked in the last-named tract than in either of the other two. Very few recently-degenerate fibres could be seen in the funiculus gracilis, owing to it being extensively sclerosed. At the level of the decussation the same features as described in the above section were present. In the cervical region of the cord the recently-degenerate fibres were more scattered, and did not form such definite tracts as in the sections at higher levels. In the dorsal region

there was considerable degeneration all round the periphery of the cord, and the portions where the degeneration was of longest standing, viz., the columns of Goll, and the crossed pyramidal tracts showed fewer recently-degenerate fibres than the other portions of the cord. In the upper lumbar region the degeneration again became less, being most marked in the posterior columns and in the ventral region of the cord that lies on either side of the median fissure. In the sacral region the vacuolation, which had been a marked feature through the cervical and dorsal regions, had disappeared from all parts of the cord except the posterior columns, where it was still present to a slight degree; recently-degenerate fibres were still present both in the posterior and ventral region of the cord. In the coccygeal region a few degenerate fibres could be seen in the posterior columns at the most dorsal portion on either side of the median fissure.

Nissl method.—The cells of the cortex, pons, or medulla appeared for the most part normal; there were fairly numerous healthy cells in every region of the cord, but in the lumbar region, although they have a good nucleus and nucleolus, the cells were somewhat swollen and the chromophilic substance rather finely granular. Some of the cells were pigmented, but not to a marked degree. It is probable that there was some diminution in the number of cells in the anterior horn. The cells of Clarke's column were few in number, stained badly, and were markedly pigmented.

Van Gieson's method.—Sections stained by the above method taken at various levels in the medulla and spinal cord were examined with regard to the condition of the vessels and membranes. With regard to the latter no thickening could be found in any region of the cord; the vessels in the pia arachnoid were in some parts distended with blood, but there was no evidence either of recent or of old thrombosis. With regard to the vessels within the cord in those portions which were most affected, the vessels were often engorged, but there was no thickening of the walls or evidence of thrombosis. There was no small cell infiltration around the degenerate areas, whether recent or old.

Peripheral nerves.—The right sciatic showed marked degeneration by the Weigert-Pal method, more than one-half of its fibres having undergone degeneration. The same feature was apparent by the Marchi method, but the number of recently degenerate fibres was small, although in one bundle this was fairly marked. The right anterior crural nerve was very much better preserved

than the sciatic, comparatively little degeneration being visible by the Weigert-Pal method. By the Marchi method, however, although there was practically no recent degeneration the spacing of the fibres showed that a considerable number of fibres must have undergone atrophy. The right phrenic nerve appeared normal both to the Weigert-Pal and to the Marchi method.

Posterior root ganglion.—The cells of the posterior root ganglion were for the most part normal, although here again some were considerably pigmented, and others were shrivelled. The seventh left thoracic posterior root ganglion showed on section a small cyst measuring 3 mm. in diameter and filled with a clear fluid (plate ix., fig. 2). The walls of this cyst were laminated, the inner layer being formed of fine connective tissue and the outer layers of more closely packed fibrous tissue. Many of the cells of the ganglion appeared atrophied and pigmented, others, however, were normal. There was an increase of connective tissue between the cells. The anterior and posterior roots, both by the Weigert-Pal and Marchi methods, appeared normal.

(This case has not been examined with the completeness of the other cases owing to the fact that the patient only died shortly before the publication of this paper; but sufficient has been done to show that it was a typical case of the disease, and owing to the long third stage corresponded closely to Case No. 1 in its pathological aspect.)

Cases not Verified.

Case 8.—M. C., aged 38 years, a married woman, was admitted into the National Hospital under the care of Dr. Ferrier on September 23, 1898, complaining of weakness of the legs, numbness, and inability to walk. She had had syphilis ten years before admission, otherwise she had had good health. There was no history of alcoholic excess. Eighteen months before admission she first noticed numbness and stiffness in the calves of both legs. A few months later she dragged both feet in walking, the legs were stiff, and she had a tight girdle sensation round the waist. These symptoms gradually increased until six weeks before admission, when, in the course of one day, she became entirely unable to stand. With this she developed retention of urine (she had had slight precipitancy of micturition ever since the beginning of the illness).

Her doctor informed one of us (J. C.) that a month before admission he had examined her, and had found the knee-jerks brisk and double foot clonus present.

When admitted she was a very pale, sparely nourished woman; the mental state, speech, articulation, special senses, optic discs and cranial nerves were normal. There was slight lateral nystagmus. The upper extremities and trunk were normal as regards motion. The lower extremities were well nourished and were flaccid. She could execute all movements of the lower extremities against fair resistance as she lay in bed. On attempting to walk, supported on either side, the feet were poorly lifted, and she was wildly ataxic. When standing supported much *danse des tendons* appeared. She fell at once when unsupported. The electric excitability of the muscles was normal. There was slight blunting of sensibility to touch and temperature, but not to pain over the lower two lumbar and all the sacral areas. Sense of passive position was entirely lost in the lower extremities, and was very much impaired in the wrists and fingers. The sphincters showed alternating retention and precipitancy.

Reflexes.—Wrist and elbow-jerks brisk. Knee-jerks absent. General reflex excitability of the lower limbs increased. Plantar reflexes showed extensor responses.

Blood count: Hæmoglobin 60 per cent. of the normal; red blood-cells 4,900,000 per cm.; no nucleated red corpuscles; white blood-cells normal. Spleen not enlarged. Other organs healthy.

She left hospital a month later, her condition not having changed. A month after leaving hospital she developed complete anæsthesia and severe œdema of the lower extremities, which became completely paralysed. Bedsores developed, and she died a month later.

No autopsy was performed.

Duration of illness—twenty months; stage of slight ataxic paraplegia—sixteen months; stage of severe paraplegia—two months; stage of flaccid palsy, absent knee-jerks, and œdema—two months.

Case 9.—H. T., a dressmaker, aged 30 years, was admitted into the National Hospital under the care of one of us (J. S. R. R.) on October 31, 1899, complaining of numbness and weakness of the legs, sphincter trouble, and anæmia of one year's duration.

There was a family history of rheumatic fever. She had never been strong, and had frequently suffered with dyspepsia and anæmia. A year before admission she noticed that she was unsteady when walking in the dark, and she became very pale. This was followed by numbness in the legs, which became stiff

and dragged when she walked. She got about till nine months later, when she became much worse, and was unable to walk. Numbness in the tips of the fingers and a girdle sensation then appeared. She became very breathless and pale, but had no hæmorrhages. Ten days before admission she developed complete incontinence of both sphincters.

When admitted she was an extremely anæmic, sparely-nourished girl. Her mental state was weak and emotional. Speech was normal, but her voice was low pitched, and she did not control the blast of air properly. She had been deaf in the left ear for ten years and had tinnitus on that side; otherwise the special senses were normal. Optic discs and cranial nerves (except tenth and eleventh) normal; the pupils were normal; there was slight lateral nystagmus. There was general paresis of the left vocal cord. The trunk muscles were normal. Movement of the upper extremities was generally feeble, and there was distinct ataxy in both upper limbs. All movements of the lower extremities were very feeble. She could just stand when supported on both sides. Great rigidity of the legs and some general wasting. The faradic excitability was diminished. Marked flexor and adductor spasm. There was slight numbness in the finger tips of both hands and a tight girdle sensation round the lower part of the abdomen. There was marked impairment of sensibility to all forms below the root level—nowhere absolute. Severe dull pain in left hypochondrium.

Reflexes.—Jaw-jerk not obtained. Wrist and elbow-jerks exaggerated; knee-jerks exaggerated; double foot clonus. Superficial reflex excitability of the lower extremities much increased; plantar reflexes were brisk extensor responses; abdominal reflexes absent. Complete incontinence of both sphincters. Spine normal. Heart: Loud basic systolic murmur; *bruit de diable*. Liver and spleen not palpably enlarged. Some soft œdema of lower limbs and back. Blood count: Hæmoglobin, 68 per cent.; red blood cells, 4,700,000 per cm.; a few nucleated red cells present; no poikilocytosis; marked lymphocyte leucocytosis. The temperature ranged between 99° and 102° F.

This patient subsequently developed patches of herpes over the fifth left dorsal root area, and the anæsthesia crept up to the upper limit of the seventh cervical root area.

On November 17 the blood was again examined, with the following result:—Red blood cells, 3,708,000 per cm.; white blood cells, 7,000 per cm. No nucleated red cells. Differential leucocyte count:—(*a*) Polymorphonuclear cells, 71 per cent.; (*b*)

lymphocytes, 23 per cent.; (*c*) hyaline cells, 3 per cent.; (*d*) coarse oxyphile cells, 1·2 per cent.; (*e*) basophile cells, 0·6 per cent.; (*f*) cells with reniform nuclei, 1·2 per cent.

We are much indebted to Dr. A. G. Phear and to Dr. A. J. Whiting for valuable assistance in examining the blood of this patient.

Case 10.—A. T., a married woman, aged 37 years, was admitted into the National Hospital under the care of Dr. Buzzard on February 6, 1900. She complained of weakness and numbness in the legs and arms and inability to stand of seven months' duration. There was no history of syphilis or of alcoholism.

Seven months before admission she noticed that the feet were numb and slightly swollen. Soon afterwards the legs gradually became stiff and dragged when she walked, sometimes giving way at the knee. She did her work for five months. Two months before admission she became unable to stand and her arms became weak. She had had no ocular or sphincter trouble and no pain.

When admitted she was a well-nourished woman, not obviously anæmic. Mental state intelligent. Speech, special senses, optic discs and cranial nerves normal. There was slight incoordination in both hands, but no weakness or wasting. The trunk muscles were normal. All movements of the lower extremities were performed with considerable power, but with great incoordination. She could only stand when supported on both sides, and made the wildest excursions with her legs in attempting to walk. There was no wasting, and the electric excitability was normal. She complained of numbness in the legs and fingers. She could not recognise light touches below the fourth lumbar root level. There was no sphincter trouble. The wrist and elbow jerks were difficult to elicit; the left knee-jerk was obtained with double reinforcement; the right was absent. The plantar reflexes showed a brisk extensor response.

Case 11.—J. M., a married woman, aged 54 years, was admitted into the National Hospital under the care of Sir William Gowers on August 4, 1899, complaining of weakness of the legs and of tingling and numbness in all four extremities. Her health previous to this illness had always been good. She had led an irregular life as an actress.

Two years before admission she had an attack of inflammation of the eyes, and herpes appeared all around the right eye. Shortly after this the legs and the fingers became numb; she had burning

pain in the feet and a feeling as if she was walking on cotton wool. The legs slowly became stiff and she dragged them. The numbness spread slowly upwards, and she had a tight girdle feeling at the level of the umbilicus. She became very unsteady in walking.

Four months before admission she developed ptosis on the right side which passed off in a few weeks.

A month before admission she began to have difficulty in passing urine.

On admission she was a well-nourished, pale, sallow-complexioned woman. Mental state and speech normal. Smell was very defective in both nostrils, but otherwise the special senses were normal. The pupils were equal and reacted normally. The cranial nerves were normal to objective tests, but she stated that her voice in speaking and in singing had deteriorated very much during the year preceding admission. All movements of the upper extremities were powerfully performed, but with some incoordination, and there was some tabetic athetosis when the hands were held out and the eyes shut. The lower extremities were weak in all movements and there was marked ataxy. She could only stand with support on both sides, and on the attempt to walk the feet were raised high and placed down forcibly and in any position. The abdominal muscles were very weak, and she could not raise herself into the sitting position without assistance. There was marked diminution of sensibility to all forms below the ensiform process. The same diminution was found over the hands and ulnar borders of the forearms. She complained of a sensation like iron bands round the pelvis and abdomen as high as the lower costal margin. There was complete loss of sense of passive position in the lower extremities and marked loss in the hands. There was occasional incontinence of urine and constant delayed micturition. Wrist and elbow-jerks present and equal; knee-jerks increased; double foot clonus and the plantar reflexes showed the extensor response. Blood count: red blood-cells 4,300,000 per cm.; hæmoglobin 80 per cent.

Case 12.—W. P., a scene-shifter, aged 45 years, was admitted into the National Hospital under the care of Dr. Ferrier on March 21, 1898, complaining of weakness of the legs and of the right hand. Family history and previous health good. He was a scene-shifter, and worked in an atmosphere laden with colour dust from the scenery. He denied venereal disease. He was in the habit of taking a good deal of alcohol.

Seven weeks before admission he noticed a numb cold feeling in both feet, which rapidly spread up to the waist. The legs

then became weak and stiff, and he dragged them in walking. Sudden flexor spasms in the legs troubled him at night. Six weeks later he was much worse, and the right hand became very weak. Sharp stabbing pains in all four limbs troubled him greatly.

On admission he was a strongly-built man; cranial nerves and special senses normal. Great weakness of both hands R. > L. Abdominal muscles so weak that he could not sit up in bed. Absolute paralysis of the right leg and almost absolute paralysis of the left leg. No wasting. Complete loss of sense of passive position in the lower extremities. Relative anæsthesia to all forms below the umbilicus. Sphincters normal.

Reflexes.—Knee, wrist, and elbow-jerks exaggerated; double foot clonus. Plantar reflexes brisk.

Skin of the feet thin and shiny. Temperature 98° F. to 100·5° F.

On the ninth day after admission the temperature rose to 103° F., and complete paralysis of the legs, complete incontinence and profound anæsthesia appeared. Two days later the knee-jerks were lost, and marked vaso-motor paralysis and œdema set in. He remained for a week in an apparently moribund state, with muttering delirium, and developed a right-sided pleurisy and a large sacral bedsore. At the end of this time he began to improve rapidly. The temperature fell. The anæsthesia and incontinence disappeared. The bedsore healed, and the spastic symptoms returned to slowly disappear in the course of the following two months.

At the time of writing this patient is at work, and the only sign of his illness that remains is the scar of the large bedsore.

During the acute stage of his illness he was treated with iodide of potassium and strychnine. During the last year he has had five epileptic attacks, never having previously had an attack.

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THE PATHOLOGICAL FINDINGS IN A CASE OF GENERAL CUTANEOUS AND SENSORY ANÆSTHESIA WITHOUT PSYCHICAL IMPLICATION.

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THE detailed clinical history of this case can be found in BRAIN (vol. xiv., 1891, part iv., page 44). A careful search of the medical literature has disclosed no similar instance occurring either before or since the date of its publication.

A synopsis of the clinical record as then published shows:—(1) A strong hereditary tendency to nervous instability, the mother, two maternal uncles, two brothers and two sisters having been insane. The father had died of tuberculosis. (2) A syphilitic infection acquired from her husband at the age of 29 years, subsequent to which the patient had several abortions, sore throat and falling out of the hair.

For twenty-two years, after the subsidence of acute symptoms due to the syphilitic process, there was fair health. Then came an attack of acute arthritis, after which the patient never fully recovered her former physical condition. Within a few months thereafter her eyesight began to grow dim, there were sudden flashes of light before the eyes, and vision was gradually extinguished, only sufficient remaining to enable her to distinguish light from darkness.

In the early summer of 1889 (nearly six years after the rheumatic attack) the patient began to experience a general tingling and formication in the skin of the entire body, which was shortly followed by several spells of uncontrollable vomiting.

A consensus of the numerous examinations made during the years 1889 and 1890 showed a total loss of thermic, pain, olfactory, gustatory, equilibrium, pressure and weight sensa-

tions; almost total loss of the visual sense, and a partial loss of tactile and muscular impressions, muscular sense and auditory perceptions. None of the special senses or cutaneous sensations remained wholly uninvolved.

Besides these disturbances of the sensory apparatus, several other symptoms of almost equal prominence were recorded.

The musculature, while responding to the will, did so in such a feeble manner that the patient was incapacitated from helping herself to any extent. Thus the dynamometer, when taken in the hand and squeezed, was so feebly compressed that the indicator showed no movement of the dial, though the woman exerted every effort in the trial. Despite this fact, however, both nerves and muscles responded promptly to the galvanic and faradic currents, nor was there anything abnormal noticeable about the quality or time of the reactions.

The cutaneous reflexes were all abolished. The faucial and pharyngeal reflex movements were absent, and a sound could be passed over the epiglottis into the larynx without eliciting a sensation of discomfort or inducing cough. During the attacks of vomiting there was no sensation of nausea.

When first examined the knee-jerks were present and normal. The biceps-jerk could also be elicited with some little trouble. The reaction of the abdominal muscles was lost, and the ankle beat was feeble. By the middle of July, 1890, the right knee reflex had disappeared, and the left one was weak. All other reflexes, deep and cutaneous, had been completely abolished. A year later the jerk of the left patella tendon was found to be extinguished.

Furthermore, with auditory perceptions a progressive dulling could be noted. When the woman was first admitted to the hospital the sense of hearing was fairly acute in both ears. Gradually the difficulty in receiving auditory impressions increased, until finally the voice could not be heard except with strenuous effort.

The ophthalmoscopic examination showed an extensive choroiditis pigmentosa, with atrophy of the optic nerves. Only a few vessels could be seen in the retina, and these

were of minute size. In both lenses there was a beginning cataract.

Whether the optic nerve atrophy should be considered part of the general disease-process, beginning as it did long before the other symptoms, is somewhat problematical, though in tabes the same trouble is not infrequently noted as a forerunner of definite symptoms of the disease.

The pupils were at first in a state of mid-dilatation, and responded slowly to light, direct or reflected. They did not dilate on irritation of the cervical sympathetic. At a later stage the pupils became somewhat narrower, but remained sluggish to stimuli.

There were a number of interesting disturbances of the glandular secretions. During the fall of 1889 the mouth was found to be almost absolutely dry, the tongue heavily cracked, the epithelium eroded from its tip and sides, while the entire buccal surface was red and congested. At the same time the secretions of the lachrymal glands had almost ceased, the surfaces of the conjunctivæ being dry and injected. The skin was also dry and devoid of odour. After a course of potassium iodide these phenomena slowly abated, and the secretions returned to a more normal state.

Various unusual sensations troubled the patient at times. Cramps of the gastrocnemii, sensations of burning between the scapulæ, a girdle feeling around the abdomen, and neuralgic twinges in the nerves of the extremities were often complained of. Occasionally there were chronic fibrillary spasms of the small muscles of the thumbs.

Attacks of diarrhœa, refractory to treatment with drugs, though yielding to a continued milk diet, occurred in the latter part of the winter of 1890. These were, on several occasions, followed by a protracted vomiting, without pain or nausea.

Trophic symptoms in the form of a bulbous appearance of the finger tips and ridging of the nails, together with purpuric spots, developed late in 1891.

Throughout the long course of the illness there was never the slightest departure from normal mentality on the part of the patient; no hysterical attacks, no pathologica

depression or exaltation, and no delusions or hallucinations were ever noted. A slight apathy was the only perceptible change in the mental phenomena, but this was not greater than is frequently noticed in those who have become blind and helpless.

In discussing the etiology of the sensory phenomena in the previous article, three possibilities were suggested. (1) That the malady was functional, an opinion largely influenced by the pathological findings in the three autopsies on cases of general cutaneous and sensory anæsthesia reported by von Ziemssen, Krukenburg and Schüppel, respectively. This view was held to be hardly consistent with the presence of an optic neuritis, loss of the reflexes and the trophic manifestations. (2) That the case was an obscure instance of syringomyelia, or (3) that the terminal end-apparatus of the peripheral nerve fibres was diseased.

Though many points are not cleared up by the autopsy and the subsequent microscopic examination of the tissues, the results obtained are sufficient to show that none of these explanations would hold good, the nearest approach to a correct diagnosis being found in the last conjecture—disturbance of the peripheral nervous system.

The patient's condition did not materially alter after the record of the case was published. The anæsthetic and other symptoms, from the reports of the house physicians to the hospital, remained about stationary, and, on the rare occasions on which I saw her, there were no additional phenomena to be noted other than a steady though slow decline of the vital powers. Late in the year 1893 another ophthalmoscopic examination was made by Dr. H. Friedenwald, who found in the left eye an extensive and typical retinitis pigmentosa, the papilla being blurred and of a dirty yellow colour. Few vessels could be noted. In the right eye the clouding of the lens was so profound that the retina could not be seen.

About the middle of May, 1898, Mrs. R. became slightly lethargic, a condition that slowly increased to coma, in which state she died on the 25th of the month.

The *autopsy* was performed ten hours after death, the

body being still warm to the hand. The cadaver was not emaciated, and *post-mortem* lividity was visible only on the dependent parts of the back. Both pupils were strongly contracted, though the right was much smaller than the left, being a mere pin point opening. There were no iritic adhesions. The nails were ridged longitudinally. Rigor mortis was present in the extremities. No local atrophy of the muscles could be noted.

The cranial cavity was first opened. The bones were dense in texture, and somewhat thickened, measuring 10 mm. in the frontal, and 8 mm. in the occipital regions. No diploë were seen anywhere within the cut bones. The marking of the blood-vessels on the inner surface of the parietalia was quite deep. The dura was slightly adherent to the bones along the vertex. The Pacchionian granulations were enlarged and quite granular. The longitudinal sinus contained a small quantity of dark fluid blood, but no clots. The lateral sinuses were empty of blood. The dura mater was not thickened, nor adherent in any way, except for the slight adhesions already mentioned. About 50 c.c. of slightly blood-stained serum escaped when the sub-dural space was opened.

The pia mater was moderately thickened, the meshes being filled with a straw-coloured gelatinous material. Its veins were filled with dark fluid blood. Along the border of these vessels lay broad white lines marking the distension of the lymph spaces. This distension of the lymph channels did not extend along the arteries at the base. The thickening of the pia was greater in the parietal than in the frontal and occipital regions. In the right sulcus of Rolando there was a much heavier deposit of the gelatinous substance than on the opposite side.

The cranial bones of the vault were normally symmetrical, those of the basis cranii a little contracted.

Basal Vessels.

The vertebrals were normal in calibre, but each of them showed, 27 mm. below their union into the basilar, a small

aneurismal dilatation. The posterior cerebellar arteries diverged from the parent stem at the usual place of departure and were normal in calibre. The middle cerebellar on the left side was normal in position and size, while the one on the right side was rudimentary. The anterior cerebellar arteries were normal in calibre and disposition. The posterior communicating arteries of the circle of Willis had a calibre only sufficient to admit a fine pin. The Sylvians were normal both as to their size and the distribution of the main branches. Both anterior communicating, as well as the anterior cerebrals, were of fair size. Scattered over the basilar, the anterior communicating, and Sylvian arteries, were a number of atheromatous patches of moderate diameter, but the arterial stems showed but little thickening, the majority collapsing when cut across.

The encephalon, inclusive of the soft meninges, weighed 1095 grammes. The thickened and vascular pia stripped off without detaching any bits of the cortical substance. But few of the larger arteries of the pia showed the presence of marked atheromatous changes.

Left Hemisphere.

The sulci and gray matter were of normal depth and fair development. The five primary fissures were typical in configuration. The pre-central fissure was bridged in two places by unusually broad bands of cortical substance. The convolutions of this hemisphere were small, rather intricate, but corresponded to the usual types.

Right Hemisphere.

The convolutions and fissures of this hemisphere were symmetrical with those of the left side, except that the anterior central convolution was much broader. The right optic nerve, on measurement, was slightly smaller than the left, though the difference was trivial. To the eye these nerve tracts afforded no evidence of gray degeneration.

On section of the hemispheres, the ganglia, the corpus callosum and the other inter-hemispheric bands, as well as

the white matter, disclosed no evidence of disease. The choroid plexuses contained a number of small cysts.

The cerebellum weighed 140 grammes. There were no pathological changes to be discovered in it.

Macroscopic examination of the medulla and pons Varolii was distinctly negative in respect to naked eye lesions. The membranes around the medulla were a little thickened. The pyramids in the medulla were symmetrical.

The entire cord with the membranes and filum terminale were removed, but none of these structures showed any vestige of a diseased condition.

Thoracic Cavity.

The strands and ganglia of the cervical sympathetic nerves were in every respect natural. The lungs were normal. The pericardium contained a minimal amount of fluid. The heart weighed 250 grammes. The posterior segment of the mitral valve was much thickened. The intimal surface of the aorta was studded with deposits of calcareous material, but the vessel showed little general thickening. The aortic valves were normal.

Abdominal Cavity.

The liver weighed 980 grammes, but was structurally normal. Each kidney weighed 100 grammes. The capsules were strongly adherent to the cortical substance, and when peeled off brought with them portion of the subjacent tissue. The cortex was reduced in thickness, and the entire renal tissue was hard and resistant to the knife. The capsule over one-half of the spleen was enormously thickened, while over the other portion it was natural. The medullary tissue was normal. Pancreas, intestines, lymph glands and bladder, showed no evidence of disease.

A large number of pieces of the brain from the several regions were preserved in alcohol, formol, Müller's fluid and Flemming's solution. The entire cord was hardened in Müller's fluid and alcohol. Several bits of skin from the

neck and abdominal walls were likewise preserved in alcohol and Müller.

The spinal cord under the microscope showed the most definite alterations, and accordingly will be first described.

Lumbar Cord.

Weigert hæmatoxylin.—The nerve-bundles of the filum terminale show no lesion. Throughout the whole of the lumbar enlargement the white columns have every appearance of health, the axis cylinders being distinct, the myeline abundant, and not at all varicose. In the gray tracts, the finer fibres inclusive of the commissural are well stained and show no indication of degeneration. Neither the anterior nor posterior root fibres have any signs of pathological change, although there is considerable thickening of the pia around them. The cells of the anterior horns are fairly numerous. Some of them contain heavy depôts of pigment granules, while others are entirely free from the metaplastic material.

Dorsal Cord.

The lowermost portion of this segment is equally free from signs of disease in the medullated tracts, except that the posterior commissural fibres are not so numerous as in the lumbar regions. When, however, the level of the ninth dorsal vertebra was reached, a small area of degenerated fibres first becomes visible in the right column of Burdach, in close proximity to the Goll column. This area is very small. It is at first entirely separated from the pia, but soon approaches it more closely, and finally touches the free margin. The form of the degenerated tract is irregularly pyramidal in shape, the base broad lying upon the external margin, the apex, sharply defined from the undegenerated tissue, penetrating more deeply. This degenerated area contains few normal fibres, and none at all in the central and apical portions. They become more abundant as the margin of the column is reached. The majority of the nerve-tubes

within the altered tract are much atrophied, with here and there an enlarged and varicose axis-cylinder among them. The root fibres at this level of the cord show no distinctly degenerated tubes, but contain more than the usual number of fine fibres that take the Weigert stain imperfectly. All medullated tracts within the substance of the cord are definitely normal, except that the bundles composing the posterior commissure are scanty.

A few millimetres above the beginning of the degeneration in the posterior column (at the lowermost border of the seventh dorsal vertebra), a new area of degeneration is seen,

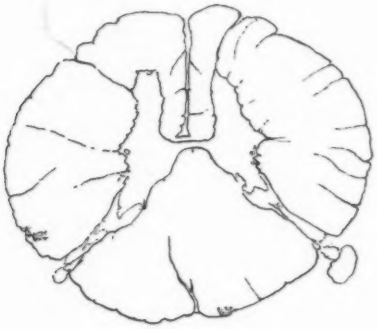

FIG. 1.

Outline drawing of a transverse section of the upper portion of the dorsal cord, showing the location of the degenerated areas in the posterior and postero-lateral columns.

this time in the left postero-lateral column. At first it appears, under a magnification of 80 diameters, as a circular patch not larger than the head of a pin lying close to the Lissauer zone, though not within the indirect pyramidal tract, and well separated from the external border of the cord. Very shortly it enlarges and assumes a wedge-shaped appearance, having its broad base on the external border of the cord and its apex toward the deeper regions, and lies within the direct cerebellar fasciculus. This area

contains a scattered number of apparently normal fibres interspersed among the sclerotic ones.

The root fibres, both anterior and posterior, show the same general conditions as those a few centimetres lower, nor do the posterior fibres that have entered the root zones, with a few exceptions, exhibit other than normal conditions. The interior medullated tracts, except those already mentioned as degenerated, the finer fibres of the gray horns, the commissural fibres, are all apparently sound. The posterior commissural fibres are again deficient in numbers.

Lowermost Cervical Cord.

The appearance of the degenerated tracts is the same as in the higher dorsal levels. As higher regions are reached the degenerated area in the right Burdach column soon begins to alter in size, and eventually entirely disappears before the beginning of the cervical enlargement is reached.

The sclerotic area in the left postero-lateral column on the other hand constantly broadens, and at the same time

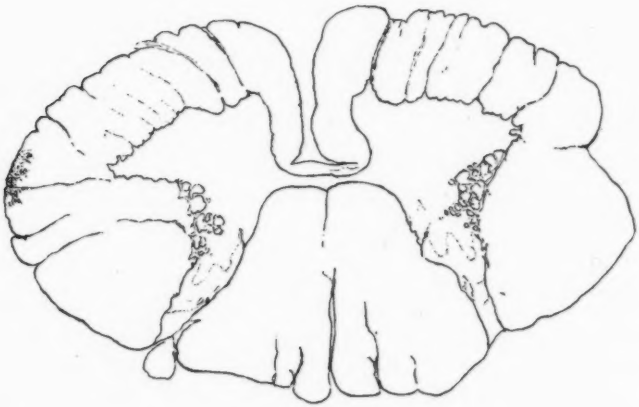

FIG. 2.

Outline drawing of a transverse section of the cervical cord above the middle of the enlargement, showing the changed position of the lateral sclerotic area.

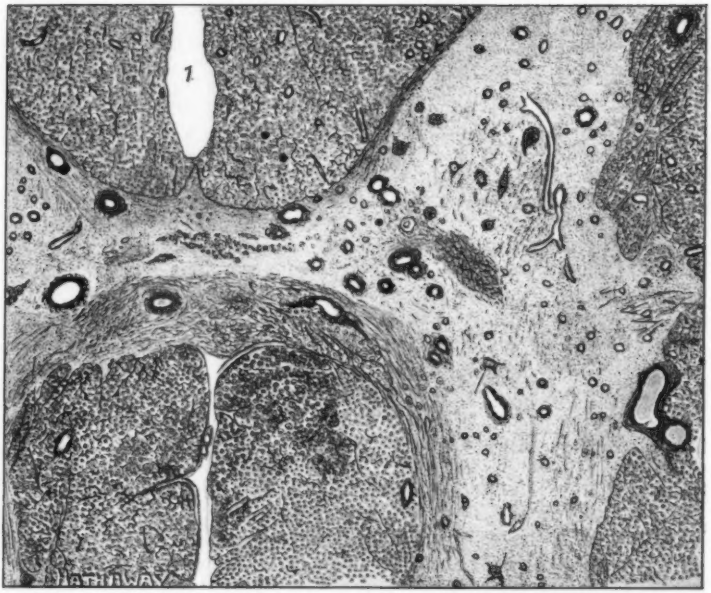

FIG. 3.

Transverse section of the dorsal cord, showing numerous thickened vessels in the neighbourhood of the commissure and adjacent gray matter. Enlarged about forty diameters.

moves from the posterior regions of the column to a position almost in the middle of the lateral region, occupying a place along the posterior edge of the Gowers' tract. Normal medullated fibres within its borders are few, the whole area being filled by dense sclerotic tissue. The wedge shape of the sclerotic zone is retained throughout this level, the borders of the degenerated being sharply defined from the normal tissue.

Cervical Enlargement.

The single area of degeneration at this level exhibits no deviation in size or appearance from that described for the lower cervical region, nor do the other columns, root-fibres, or fine bundles and single fibres of the gray matter show any departure from the normal, beyond that again the posterior commissure has almost no fibres in it.

In the uppermost portion of the cervical cord the degenerated tract spreads out a little towards its anterior boundary, and at the same time comes more directly into the Gowers' column; then at the level of the pyramidal decussation it becomes smaller, and is at length reduced to a narrow band along the anterior border of the cord, completely within this tract. The sclerotic area now rapidly decreases in size, and finally becomes lost at the level of the uppermost portion of the decussation; no degenerated fibres being evident in the direct cerebellar tract, or extending in the direction of the nucleus lateralis. The cells of this nucleus are numerous, not atrophied in the least, and do not differ in any way from those in the adjacent nuclei of origin.

Sections were made through the pons up to the level of the exit of the fifth pair, but without discovering any further traces of degenerated fibres. All the roots of the cranial nerves, with one exception, contained apparently healthy fibres. This was in a small bundle running in the right eleventh nerve, in which there was a considerable increase of connective tissue fibrillæ and a few degenerated medullary fibres, in all probability owing to the closure, from

hypertrophy of its tunics of the lumen of a local artery passing through the nerve bundle.

The Marchi preparations, for some unknown reason, did not take the stain perfectly, and all that could be determined from them was that a few isolated nerve-fibres of the posterior roots, both internal and external to the substance of the cord, as well as a few fibres of the anterior roots, took the black colour.

The Optic Nerves.

Weigert hæmatoxylin.—The blue-black staining of the myelin was hardly taken at all by the sections of these nerves. To provide against errors, other sections were again stained by the same procedure, but the result was identical. Faint bluish lines are here and there seen in the nerve-bundles, with now and then a more distinctly stained tube scattered among them. Between the atrophying nerve-fibre bundles thick masses of a coarse fibrillated connective tissue have penetrated, which are tinged a brownish shade by the hæmatoxylin. Between the individual nerve-fibres are finer strands of connective tissue elements, derived from the thicker bundles. Both optic nerves are equally affected in the degeneration, and but few nerve-fibres in either of them have escaped total destruction.

In the optic tracts the vessels, arteries and veins are everywhere greatly thickened, the muscular coat being altered as in the segments of the cord, and almost to an equal degree. The meninges around the optic nerves are not perceptibly hypertrophied or filled with nuclei, though they contain many diseased vessels.

Internal Capsule and Basal Ganglia.

Weigert-hæmatoxylin.—The nerve-fibres are distinct and well stained by the hæmatoxylin, and show neither diminution of their numbers nor atrophy of the myeline sheath, which is abundant and not varicose. The capillaries are distended with blood. The veins are dilated, but hold

little blood. The arteries, for the most part, are nearly normal; here and there is one showing distinctly the lesions of the muscularis, to be presently described.

At the level of the exit of the fifth pair, and close to the ventricular margin, a number of hæmorrhages, extending beyond the extravascular sheath into the nerve tissues, were also found; but in these the corpuscles retained their form, and the vascular rupture had probably taken place just before death.

The Pia Mater Spinalis.

The soft membrane throughout the length of the cord is thickened, but much more in the lower dorsal region than above or below it. This hypertrophy of the membrane consists chiefly in a simple overgrowth of the connective tissue trabeculæ, without any nuclear proliferation. The arteries and veins contained in the pia are all immensely thickened, but this alteration varies considerably in its histological characters in different vessels. In the largest arteries—for example, in the arteria spinalis anterior—the intima is approximately normal, while the muscular lamina is greatly thickened. In this latter layer the nuclei are too numerous, though for their kind perfect in form and staining; but among them those conforming in appearance to the usual nuclei of smooth muscle cells are seldom seen. The adventitia is not disturbed either in respect to its nuclei or the connective tissue fibres.

In a few large arteries running lengthwise in the cord's envelope, the endothelium and fenestrata have separated from the muscularis, probably a *post-mortem* change, while the latter layer has assumed a coarsely fibrous aspect, and holds but few nuclei of any kind. The fibres making up the former muscular layer are arranged in a wavy fashion, resembling to some extent the infoldings of a fenestrata, and on a superficial examination the whole layer might be mistaken for a multiplied elastica. That such is not the case is readily determined by the fact that a perfect lamina is often found internal to the fibrous layer.

In not a few of the moderate-sized arteries the lumen is closed completely, solely from the overgrowth of the middle layer. The fibrous tissue shows no evidence of hyaline degeneration with picric acid.

The contents of the lumen of such vessels as are not obliterated is not uninteresting. With eosin-hæmatoxylin, or the van Gieson stain, the whole canal is seen to be filled with a material containing no blood corpuscles and homogeneous except for a faint granulation. In preparations by other stains the homogeneous substance is found to contain a few epitheloid cells with a round nucleus.

The smaller arteries also present considerable variation in their structural conditions. A majority have their walls thickened in the same manner as in the larger vessels, while in others there is a minor but distinct degree of hyaline degeneration of the middle lamina; it now assuming a yellow-brown tint with picric acid fuchsin. When there is hyaline alteration, the nuclei are sparse and deformed. In a few arteries the elastica is reduplicated, or even quadruplicated, and at the same time the lumen is narrowed so as to be completely obliterated, or the small opening internal to the intima is filled with a mass of epitheloid cells, in which stainable nuclei are uncommon.

The walls of the veins are almost equally as thick as those of the arteries, but in the place of having the lumen narrowed it is dilated, and the outline is often irregular.

The root-fibres contain thickened vessels, some patulous, others obliterated. Numbers of the vessels among the root-fibres showed a considerable degree of hyaline degeneration. Nowhere do the nerve-bundles show any great augmentation of the connective tissue elements. The axis-cylinders are often fully stained by the aniline dyes used, and are apparently perfect.

At one point surrounding an artery coursing longitudinally in the meninges, just outside the posterior external field of the left Burdach column in the lower dorsal cord, lies a nodule of partially disintegrated round cells which bears much resemblance to a gummatous neoplasm, which, after growing to a certain extent, had degenerated. The extent

of this new formation is small, only running through eight transverse sections of the cord. The lumen of the artery near its centre is patent. There is a moderate polynuclear leucocytosis noticeable in the contents of the vessels. The thickened pia is nowhere adherent to the cord.

Vessels within the Cord.

Aniline stains.—The veins contain an abundance of polynuclear leucocytes. The walls of the vessels are often immensely hypertrophied, some of those in the anterior horns measuring 0·25 to 0·12 mm., and are visible to the naked eye. Others in the medullated regions are equally large. There is everywhere hypertrophy of the walls, principally of the middle layer, and at times it is difficult to distinguish between artery and vein. The vessels appear to be unduly numerous everywhere; there is no actual new formation of vessels, but the smallest arterioles, even the capillaries, are so thickened as to be unduly prominent in the microscopic field. This is more especially true for the gray horns than medullary tracts. The horns seem to be strewn with vessels of all sizes, from those visible to the naked eye to thickened capillaries. The region containing the most numerous diseased vessels lies lateral, on both sides, to the gray commissure, and in Clarke's columns.

The diseased arteries and veins are all of one type. The intima is but slightly affected, a little thickening of the sub-endothelial tissue being now and then noted, resulting in some irregularity of the lumen; but it is upon the media that the greatest stress of the disease has fallen. This layer is greatly thickened, and presents either a fibrous or hyaline appearance, according to the duration and intensity of the disease-process, the hyaline apparently preceding the fibrous change. In some of the vessels the peculiarly-shaped nuclei of the muscular tissue are to be seen at infrequent intervals, distorted and shrunken to such an extent as to be hardly recognisable. In others no nuclei at all are to be found, and the lamina, though fibrous, is homogeneous in char-

acter. With the van Gieson stain, the media of a number of vessels takes on a red colouring, but this is diffuse over all the layers, and not confined to the middle one. In still others the stain acts differently. The intima and adventitia are tinged red, while the muscularis takes only the yellow of the picric acid, and appears not striated, but perfectly homogeneous.

Externally from the muscularis irregular lymph spaces are often noted, corresponding to local dilatations of the intravascular space. These sometimes contain a few leucocytes. In the adventitia around these vessels there is little or no morbid changes. It is not unduly thick or fibrous in character, and contains a moderate number of round and oval nuclei.

Eosin-hæmatoxylin preparations show essentially the same pictures of the morbid process in the vessels as the picro-fuchsin stain. The intimal alteration, however, comes out more clearly. There is distinct though slight hypertrophy of the layer, with multiplication to a limited degree of the endothelial cells. The lumina are nowhere closed, though there may be great thickening of the media. Its ring-like appearance is also rarely disturbed.

The lesions of the arterial system, while diffused throughout the entire length of the cord, are much more pronounced in the dorsal region than elsewhere, and especially in the lower portion of this tract. Accordingly, in the lumbar and cervical levels there is, by comparison, but little thickening and disease of the veins and arteries, though, in truth, the degree is very considerable.

In the extravascular spaces, especially along the edges of the adventitial layer of the vessels, there are frequent depôts of hæmatoidin *débris*, as well as a finely granular material, that takes up considerable quantities of the aniline dyes.

The walls of the vessels in the *medulla* and *pons* show in individual instances a considerable thickening, on the same order as in the dorsal cord. But while all the vessels have some disease of their sheaths, in but few of them is the disease extensive. In two large arteries running longitudinally through the length of the medulla, just beneath

the floor of the ventricle and in close proximity to the median line, an extensive hyaline thickening was noted, and around them, filling up the perivascular space, are quantities of fresh red and white blood corpuscles.

In the *cortex* and *ganglia* of the brain, arterial lesions are not profound, though here and there a vessel considerably thickened may be noted, the degeneration affecting principally the middle layer.

In the *meninges* of the brain and bulb fairly numerous thickened arteries are to be found. These are not equally distributed, but only occur now and then. The points of selection in the region of the pons and medulla for the pronouncedly altered vessels are either around the nerve-roots or between the nerve-bundles. In almost any of the cranial nerves several of these pathological vessels may be seen, but it is only now and then that a degenerated and atrophied nerve-tube is noticed in the bundle.

Arteries of the Thoracic and Abdominal Skin.

The general histology of the integument seems to have suffered no essential change, though the blood-vessels are everywhere considerably thickened. In some the morbid alteration is much greater than in others, and hyaline changes in the media are noticeable. When this occurs there is complete disappearance of the muscular elements and their nuclei. The endothelial and sub-endothelial structures are also slightly hypertrophied. The nerve-bundles—so far as could be determined with the fuchsin stain used—presented no departures from the normal.

Nerve-cell Bodies.

Alcohol hardening and hæmatoxylin-eosin stain.—The nerve-cells of the anterior horns show about the same condition on the two sides. There is an advanced metaplastic change in the substance of the elements, but this is hardly beyond what one might be led to expect from the moderately

advanced age of the individual. The Nissl-bodies in the non-pigmented portions are distinct and rather coarse in appearance, and are arranged somewhat irregularly in the cytoplasm.

The nucleus is sometimes very distinct, sometimes of normal outline and contents, while at others it is indistinct. A few of them are stained very deeply, and the contour is irregular and roughened. The nucleolus in the majority of the well-defined vesicles is not altered in outline, but accepts acid stains in preference to the basic hæmatoxylin and other dyes, standing out as a bright red spot in the centre of the nucleus. The position of the nucleus is usually central.

In the columns of Clarke the pigmentary changes in the nerve-cells are greater than elsewhere, and attain a pathological degree; and, besides, there are a number of cells that have undergone simple atrophy, having shrunken to a small mass in one corner of the peri-cellular space. These atrophic cells are more numerous in the lower dorsal region of the cord than in the lumbar, upper dorsal, or cervical regions. The small nerve-cells in the posterior horns by this method of staining show no definite alteration. The cells in the lateral regions of the gray horns have few departures from the normal.

Safranin staining.—Many of the cells in all the anterior regions of the gray horns, but particularly in the columns of Clarke, are completely filled with coarse yellow pigment granules, among which a shrunken nucleus is now and then demonstrable. No nucleolus is visible in the atrophied vesicles. In rather infrequent instances the nucleus is pushed to the extremity of the cell.

In the cells that have no well-marked accumulation of pigment granules in them the Nissl-bodies are coarse, do not retain their usual arrangement, but are irregularly distributed through the protoplasmic substance. They also, at times, show a tendency to group together at the periphery of the cells, leaving a clear ring of considerable size around the vicinity of the nucleus. At other times there are scattered clumps of granula in the protoplasm. Among

the better preserved cells are some that are shrunken to a small mass of finely molecular material in which neither nucleus nor nucleolus is visible.

The state of the nucleus varies considerably in the least damaged cells. In a majority caryoplasm and chromatin particles are normal, but there are also a variable number in each section in which the vesicle has the appearance of being swollen, and the caryoplasm is devoid of stainable substance. In a very few instances there is a double nucleolus marking the presence of an irritative process.

The Nissl methylene blue stain gives identically the same results as the safranin.

Upper Cervical Enlargement.

Safranin alcohol stain.—The cellular state is identical with that at lower levels. Nowhere in the white columns of the cord, with the exception of the slightly sclerosed areas, was any morbid process to be noted in the neuroglia structures or in the medullary tubes.

Nissl methylene blue.—The irregular disposition of the granula is shown by this method with even greater clearness than by safranin and hæmatoxylin. The tendency is always to aggregate into clumps near the periphery of the cell body. A portion of the cells, however, show a normal arrangement. The large masses of yellow pigment grains stand out in striking contrast to the blue of the Nissl-bodies. Quite often the pigment covers the nucleus. In some cells, in contrast to those mentioned, the chromophilic substance is irregularly diffused throughout the cytoplasm, and in these the ordinary appearance of the Nissl granula is lost.

Quite a number of the cells show shrinkage and irregularity in the contours of the nucleus. The vesicle also has a tendency to retire to the periphery of the protoplasm. This disposition of the nucleus is more often apparent in certain regions of the gray columns of the cords than in others. Thus in the columns of Clarke it is common, while in the ventral portions of the lateral horns it is infrequent.

Medulla oblongata. Lower regions.

Deviations from the normal in the cell body are much less pronounced than in the dorsal cord. Among the cells in the scattered nuclei of origin on the floor of the ventricle there are here and there nerve elements that show displacement of their nuclei. These are irregular, distorted, and shrunken. The lesion of the nucleus is dependent, at least in part, on a simple atrophy of the nerve-cell as the result of an imperfect supply of nourishment. The protoplasm of the cell, accordingly, shows a diminution in its bulk, with corresponding enlargement of the perivascular space. Diseased cells on the whole are not common, and few of the nuclei of origin of the cranial nerves have any considerable numbers of them.

Middle and Upper Regions of the Medulla.

Van Gieson stain.—The nuclei of the nerve cells are much more frequently displaced than lower down in the bulb, and the membrane of the vesicle is shrunken and irregular. The bodies of the cells show atrophy. In the nuclei, in the region lateral to the central V-shaped point of the ventricle, there are numerous very heavily-pigmented cells. The pigment consists of the usual yellowish-brown grains, but the whole body of the cell is filled with it, and the intrinsic nucleus is no longer visible. Some of the nerve elements are evidently in process of disintegration, and when, as is occasionally the case, their nuclei can be seen, they are shrunken and distorted. Double nucleoli are by no means infrequent in these bodies, and changes in the receptivity to dyes are noticed. The morbid process is most marked in the nuclei of origin of the tenth, eleventh, and twelfth cranial pairs. Here, accordingly, there is a more advanced degree of arterial lesion than lower in the medulla.

Safranin staining.—Some of the nuclei of the cells have local thickenings of their membranes, but the caryoplasm and nucleoli are apparently normal. In others the nucleolus

is doubled, or, when single, appears much roughened. Often the nucleus is forced to the extreme edge of the protoplasm, or even partly extrudes through its boundaries. The granular pigmentation of the cells is seen to be widely distributed, but only assumes distinct pathological proportions in the nuclei of origin, already detailed, and in the upper olivary bodies. In this last location the cells are filled to their utmost capacity with pigment and are disintegrating.

Eosin-hæmatoxylin slides give the same pictures as the safranin.

Nissl's methylene blue.—The superior portions of the olivary bodies have a pathological degree of pigmentation of their nerve cells. Elsewhere the accumulation of metaplastic material can hardly be said to be greater than is usual in persons of advanced years. In a considerable number of the olivary cells none of the blue stain is absorbed, and the granules of pigment are scattered loosely within the cell space, many of them lying apart from the main body. The Nissl granula are fairly well tinged in such cells as are not heavily pigmented. The cells of the glosso-pharyngeal nucleus have less pigmentation than any other nerve elements in this region.

Region of the Pons.

The nucleus acusticus dorsalis is heavily pigmented; all others have less of it than in the medulla. The nuclei of the cells of the acusticus are displaced, and the outlines of the vesicles are indistinct. The intra-medullary portions of the abducens nerves are normal; the axone and medullary covering being perfect in detail, as are likewise all other medullated tracts in the pons. The vessels are not profoundly diseased.

Cerebellum.

The larger arteries are thickened, but less so than in any other department of the nervous system previously studied. There is a slight hyaline degeneration of the walls of the

vessels, but no visible implication of the inner and outer sheaths. The capillaries have apparently lost their elasticity, the walls are irregular and have numerous local bulgings. Their nuclei do not take the aniline stains well, and are shrunken.

The cerebellar leaflets do not appear to be atrophied in any way, the molecular and granular layers, with the cellular elements therein contained, being perfectly well defined. The neuroglia cells of the molecula lamina are not increased in number. The Purkinje cells take the aniline and hæmatoxylin stains in normal fashion, and their branches may be traced for considerable distances from the bodies. The Nissl granula contained in them do not depart in arrangement from the customary type. Few nuclei are otherwise than perfect, and these have only a slight thickening of the membrane. The nucleus, and chromatin of the caryoplasm are perfect. The nuclei of the basket cells of Kölliker show nothing abnormal. Within the granular layer the hæmatoxylin cells are well defined and exhibit nothing pathological. The white medullated cores show no morbid condition.

Cortex Cerebri. Vascular System.

In the small arteries of the soft meninges the usual indications of a hyaline degeneration of the middle coat may be almost universally noticed, but there is little or no thickening of the layer. The outer lamina is not at all involved, and in the intima there is but an occasional trace of thickening. Calcareous plaques are absent from the medium sized arteries. The veins are dilated to a moderate extent, and are filled with blood. Their sheaths present no evidence of a morbid process.

Within the layers of the cortex the degree of vascular disease is a variable one, but is nowhere profound; indeed, it is seldom more extensive than in the majority of persons who have reached the age of 70 years, though in this particular instance the morbid process is somewhat different in character. Nearly all the medium sized arteries show

hyaline degeneration of the muscularis. This is not uniform, but is scattered in patches along the length of the vessel. In the local foci, where there is an advanced degree of the hyaline mutation, the muscularis is devoid of cells and nuclei, even the intima exhibiting shrinkage and distortion of the nuclei. In the intervals where a more normal character has been retained, the muscular nuclei are present but have slight atrophic alterations with vacuolarisation of the caryoplasm. The nuclei are fairly numerous, though they do not take up the aniline colours to any extent. A few of the vessels show some thickening of the adventitial layer, but fixed nuclear proliferation is scanty. In the greater number of the vessels the outer layer is not changed, beyond containing small quantities of hæmatoidin *débris*.

The smaller arteries and capillaries, like the larger ones, show a varying degree of disease. They are irregular in outline, their cut ends standing open as if they were ridged tubes, and for long distances their walls are devoid of nuclei. When a nucleus is seen it absorbs the aniline dye badly, and is shrunken and granular. A few vessels less seriously affected show only a moderate degree of deterioration of the nuclei, and accordingly a closer approach to a normal appearance. The larger veins are filled with blood to distension. Their sheaths are fairly well preserved, having the prevailing hyaline degeneration only at irregular places. The perivascular spaces are not dilated.

Occipital Region.

The changes in the vascular apparatus are identical with those in the convolutions bordering on the central furrows. A single miliary aneurism was discovered in the entire number of sections, and this was located in the sub-cortical white matter. One small artery stopped by a thrombotic plug was also noticed.

Nerve-cells of the Cortex.

The Nissl staining of the chromophilic bodies in the large pyramidal cells is more than fair, and the arrangement of the

stainable substance is regular. The amount of yellow pigment in the pyramidal cells is not above the normal for a person that has nearly reached the natural limit of life, and is not diffuse, but confined to one corner of the cell body. The nuclei and nucleoli are natural in appearance. With the eosin-hæmatoxylin dye the cortical cells appear to be normal. The safranin dye brings out more distinctly the atrophic changes that are incidental to the involutive period of life, but the alterations are not profound.

The neuroglia does not show any increase in the number of nuclei except along the course of a few of the larger vessels in the sub-cortical medullary tracts.

Corpora Striata and Lenticular Nuclei.

The cells in these localities are slightly more pigmented than in the cortex, owing to the more extensive vascular degeneration. The neuroglia nuclei are not increased in numbers in other localities than around a few large vessels. In the *optic thalami* conditions are identical with those described for the corpora striata.

In the vessels of the ganglia the hyaline condition of the middle coat is very prominent. In a few locations there is in addition a well-marked proliferation of the nuclei of the adventitia. The extravascular spaces are wide, and a few of them are filled by a plastic exudate that stains a faint rose with eosin. No necrotic foci were found around any of the arteries.

To *recapitulate:* The fundamental pathological basis for the various nervous phenomena described in the clinical history of the case is as follows:—(1) A hyaline-fibrous degeneration of the arterial system existed, which was not confined to the central nervous regions, but was equally evident in the roots of the spinal nerves, and in the skin tissues. The degree of alteration varied from slight thickening of the muscular layer to complete closure of the lumen from hypertrophy of the middle coat of the vascular walls. The morbid change was accordingly not uniform, but

reached its maximum of intensity in the vessels of the lower dorsal cord, the meninges of the bulb and cord, and also in certain of the root-bundles of the cerebro-spinal nerves. (2) As a consequence of the vascular lesions there were degenerations of an atrophic order in the nerve-cells of the gray horns of the cord, more particularly in those of Clarke's column, and in the medulla oblongata. To this alteration in the central nervous substance at least a portion of the various symptoms must be attributed.

Besides the principal lesions there were others of considerable, though minor, importance.

The degeneration of scattered fibres in the bundles of the spinal and bulbar nerves played some part in the general symptomatology, being shown during life by the lowering of tone as regards the innervation of the muscles, as well as by disturbances of the functions of the nerves extending from the terminal apparatus.

The sclerosis of a portion of the outer zone of Burdach's column would signify that fibres ascending through the posterior root zones were degenerated, though the small area involved determines that their numbers were inconsiderable. The lesion of the tract itself has but little significance, the fibres implicated belonging to short inter-connecting bands.

The lesion of the direct cerebellar tract is not only of more importance, but presents some rather peculiar features. The absence of the majority of the medullated fibres from the posterior commissure, over considerable regions of the medulla spinalis, favours the view that a portion of the cerebellar bundle is formed from the fibres of this commissure. The gradual change of position in the sclerotic area shows also that the fibres—at least in this instance—do not proceed directly upward in the column, but are gradually diverted as other fibres enter, and assume a more and more anterior position; and, furthermore, that a portion of the fibres are lost in the upper cervical and lower regions of the medulla, and do not proceed to higher levels. This ending of the ascending fibres has been ascertained for a part of Gowers' bundle, but is not usual in the case of the com-

ponent medullated fibres of the direct cerebellar tract. At its beginning the degenerated area almost touched the left posterior root zone, while in the upper cervical region it verged upon, if it did not enter, the area assigned to Gowers' bundle.

The total disappearance of the degenerated area at the lowermost level of the medulla may be considered to have sufficient anatomical value upon which to base the theory that in the so-called direct cerebellar tract other fibre-bundles, which are at present unknown, enter into its formation, and that these correspond more closely in their manner of terminating to the bundles of the Gowers' system than to those of the cerebellar paths. The deportment of the sclerotic fasciculus may also give rise to the supposition that we have to do here with an undescribed bundle, running from the dorsal to the uppermost cervical region.

As an explanation of the numerous symptoms of the case it would appear most reasonable to suppose the existence of a disease-process affecting simultaneously both the peripheral and central nervous systems. Assuming that the arterial lesions were of late specific origin—and of this there can be but little reasonable doubt—a chronic progressive involvement of the nutrient channels, here and there leading to marked narrowing, or even to closure, of isolated vessels, might certainly have produced just such a train of symptoms as was present. Of primary importance would be the involvement of the arteries of the anterior and posterior nerve-roots of the bulbo-spinal system, though the direct lesions of the nutrient supply to the terminal nerve apparatus, which have to be inferred as they could not be definitely determined, would be of equal value. This inference of the implication of the end-apparatus is justifiable, since the arterial degeneration in the skin was quite extensive, and whenever there is starvation of a nerve tissue there result pathological reactions, which may be manifest in a multitude of ways.

The slowly progressive character of the symptoms is also consistent with the theory of tissue starvation. All the

lesions of the nerve-cells of the cord and bulb are of this type—atrophy and pigmentary degeneration from mal-nutrition. When nutrition is at a low ebb, metaplastic granules accumulate in the protoplasm of the cell.

The condition of the optic tracts, in which the lesions are identical with those of other nerve-roots, except that they are more advanced, would argue that the thickening of the blood-vessels was of long standing, and that only when the process had advanced to an extreme degree did any definite symptoms show themselves. This is exemplified more particularly in the state of the cortex cerebri. Though in this region vascular disease was manifest and diffuse, it had not advanced nearly to such a degree as in the gray matter of the dorsal cord or in the adjacent meninges. As a consequence, the functions of the cortex, while not as perfect as in youth, were not reduced to the same low level as those of the cord and bulb.

One pathological fact should be remembered in considering the clinical symptoms, namely, that it is not necessary for a vascular lesion to proceed to such a profound degree as to cause the entire shutting off of the nutrient supply before a nerve-tissue will show signs of deviation from its normal functions. With a reduced supply of nutrient plasma definite manifestations of nervous exhaustion are brought about, and these are not due to a degeneration of the component portions of the neurone which is visible in the tissue after death, by our present methods of preparation, in the form of morbid alterations of the cytoplasm, axone or myeline. Long before this stage is reached the entire neurone is incapable of performing its natural functions in an efficient manner, and as a consequence anæsthesias, paræsthesias, diminution or exaltation of the reflexes, and dulling of the special senses may be noted. Almost precisely similar results are encountered in advanced stages of progressive paralysis, especially in the syphilitic cases, in which, when vascular lesions of the arteries of the cerebrum and cord have advanced to a profound degree, there is a gradual but progressive dulling of cutaneous sensibilities and special sensations.

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A CASE OF TRANSVERSE LESION OF THE SPINAL CORD, WITH A CONTRIBUTION TO THE LOCALISATION OF MUSCLES IN THE CORD.

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THE following case is of some importance, not only because of its symptomatology, which exemplified several interesting points, but also because the level of the injury was capable of demonstration during life by means of the X-rays and subsequently verified *post mortem* after an interval long enough to permit of the degenerations being traced with accuracy by the Marchi method. It thus affords a study of some value, both clinically and pathologically.

CLINICAL NOTES (by Dr. Purves Stewart).

The patient, K. T., a married woman, aged 28, was admitted to Westminster Hospital under Mr. Turner's charge on the morning of September 8, 1899, immediately after having fallen out of a window, a distance of about twenty-five feet. On admission she was found to be totally paralysed in the intercostal, spinal and abdominal muscles and in the lower limbs, and partially paralysed in the upper limbs, flexion and extension of the fingers being impossible. The temperature on admission was 95° F.

On examination of the patient on September 8, some twelve hours after the accident, the following observations were made:—

The patient is a well-nourished woman of good intelligence. Speech and articulation are normal. She is obviously paralysed, partially in the upper extremities, totally in the intercostal and abdominal muscles and in the lower extremities. There is

moderate anæsthesia to touch and pain on the trunk below the third ribs in front and below the spines of the scapulæ behind; also along the inner borders of both upper limbs symmetrically from the axillæ to the fingers, the upper limit of the anæsthesia running along the long axis of the middle finger in each hand (*vide* fig. 1). At the level of the nipples in front and one inch below the inferior angles of the scapulæ behind, the anæsthesia and analgesia become absolute. No hyperæsthetic zone can be detected above the level of anæsthesia.

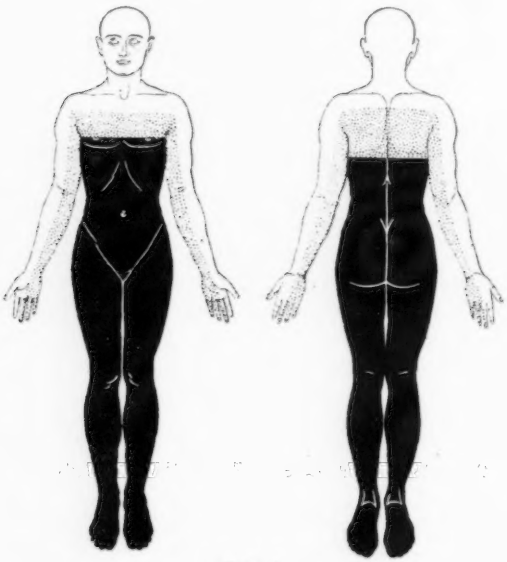

FIG. 1.
September 8.—Twelve hours after accident.

There is no evidence of paralysis of any of the cranial nerves. In the upper extremities the following muscles survive and can be voluntarily contracted on both sides, viz., *biceps, deltoid, supinator longus, flexors of wrist, extensors of wrist,* and *upper part of pectoralis major.* The following muscles, on the other hand, are totally paralysed on both sides:—*Triceps, long flexors of fingers and thumb, long extensors of fingers and thumb, interossei, lumbricales, thenar,* and *hypothenar muscles, lower part of pectoralis major.*

The fingers and thumb are persistently semi-flexed at the interphalangeal joints in both hands; otherwise the posture of the limbs is not constant or stereotyped in any way.

There is total paralysis of the intercostals. The breathing is entirely diaphragmatic and quite easy. There is no dyspnœa and the extraordinary muscles of respiration at the root of the neck are not in action.

The abdominal and spinal muscles are totally paralysed; so also are the lower limbs, which are flaccidly extended at the hips, knees, and ankles.

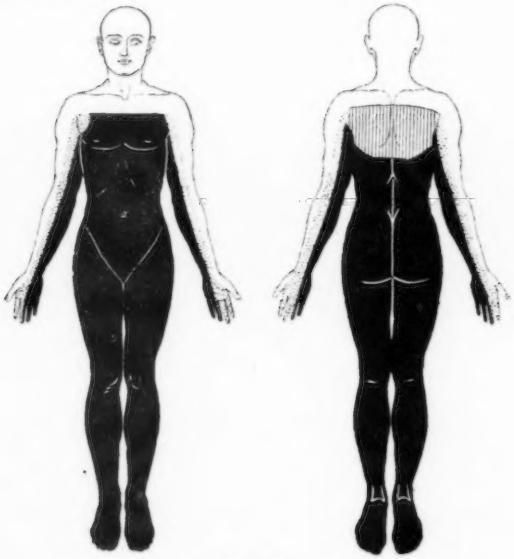

FIG. 2.

September 19—Twelve days after accident.

The knee-jerks cannot be elicited, although the vastus internus contracts to direct tapping on each side. There is no Achilles-jerk. The abdominal and epigastric reflexes are absent. The plantar reflexes are present and are extensor in type. There is absolute retention of urine, requiring the use of the catheter.

There is no tenderness in the region of the cervical spine, nor can any definite displacement of the vertebræ be detected posteriorly.

Temperature 99·4° F., pulse 84, respirations 24.

September 19 (twelve days after the accident).—The anæsthesia was again carefully observed (*vide* fig. 2), and the absolute anæsthesia was found to include the little and ring fingers and the ulnar side of the middle finger of the right hand, being less extensive on the left hand, where it only included the little finger and ulnar side of the ring finger. Slight impairment of sensation to touch, pain and temperature is somewhat more extensive than formerly, extending now as far as the web of the thumb on both sides. The upper limit of absolute anæsthesia on the trunk is still the same posteriorly, viz., below the angles of the scapulæ, but anteriorly it now extends up to the third ribs. No hyperæsthesia can be detected to light touches or pricks above the level of the anæsthesia; but the patient states that the skin in the region of the upper part of her chest feels tender when she is being washed.

The surviving muscles of the right upper extremity are stronger than in the left. Paralysis of triceps, flexors and extensors of fingers, and of intrinsic hand muscles is exactly as when she was admitted. To-day the *latissimus dorsi* was examined and was found to survive, contracting briskly on both sides when the patient coughed.

The pupils are moderate in size, equal and contract briskly to light and on convergence. They dilate sluggishly to shade.

The supinator-jerks are brisk; the knee-jerks are still absent. There is no ankle-clonus, but passive dorsiflexion of the ankle on either side produces a slow tonic contraction in the muscles of the calf. The abdominal and epigastric reflexes are still absent. The plantar reflexes both show an extensor response of the hallux. At the same time as the hallux becomes extended, the knee becomes flexed and the hip flexed and adducted. The superficial anal reflex is present on pricking the skin of the perineum. The deep anal sphincter, however, is paralysed and does not grasp the examining finger, and when the latter is withdrawn the anus remains for a time "yawning" widely open and after a few seconds it slowly closes. There is retention of urine with occasional "overflow" dribbling, which is kept in check by regular catheterisation.

All the muscles of the upper limbs, both paralysed and non-paralysed, were examined electrically with faradic shocks, and found to react normally.

An X-ray photograph of the cervical spine shows that the fifth cervical vertebra is dislocated forward on the sixth, the spinal canal being greatly narrowed at that level (*vide* plate).

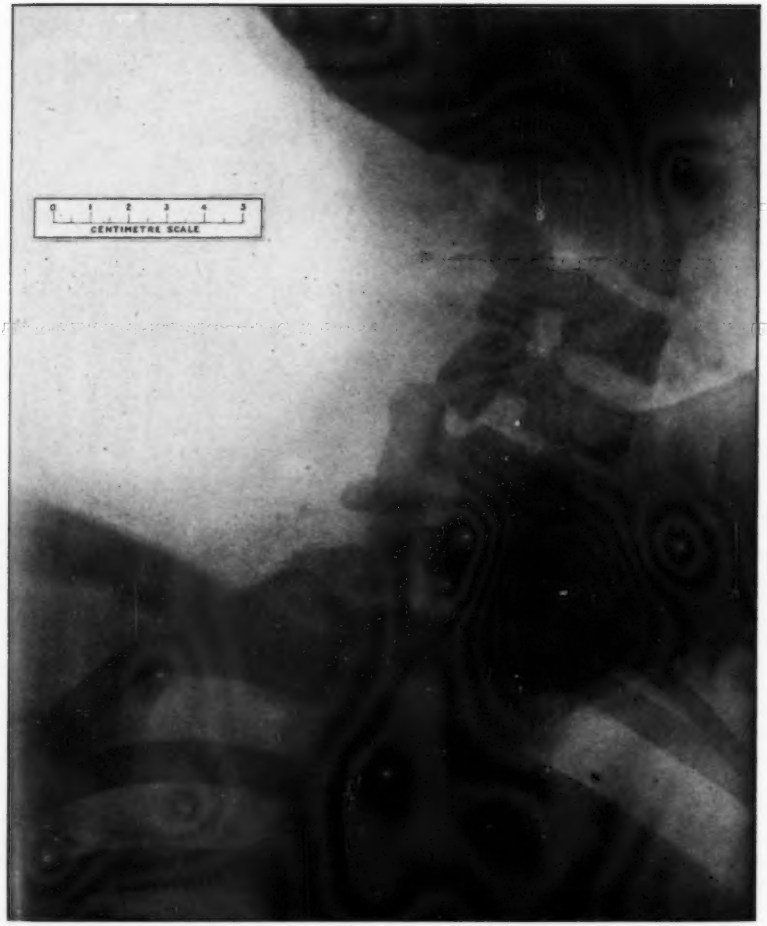

PLATE TO ILLUSTRATE DR. PURVES STEWART'S AND MR. WILLIAM TURNER'S PAPER.

September 20.—This morning, under an anæsthetic, Mr. Turner reduced the dislocation by extension. The displaced vertebra was felt to slip back into its place with a distinct jerk. Immediately before the operation the patient's knee-jerks were tested and were elicited for the first time since the accident, the left knee-jerk being extremely faint, the right a little less difficult to elicit. No Achilles-jerk on either side. Plantars still extensor in type. After the replacement of the dislocated vertebra an extension apparatus was applied with a weight of eight pounds to the head.

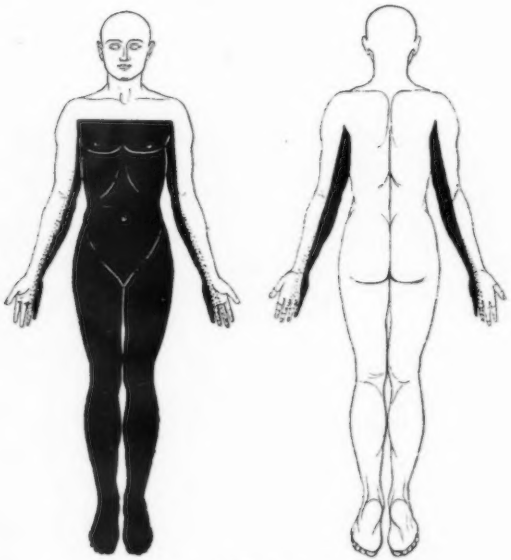

FIG. 3.

October 10.—*Permanent Anæsthesia.* A month after accident.

September 26.—Anæsthesia on front of chest same as when last noted. Upper limit on upper extremities splits the middle finger. Right arm distinctly stronger than left, though no previously paralysed muscles have yet recovered. Knee-jerks just present, the right being greater than the left, but both are very difficult to elicit.

October 10.—Surviving muscles exactly as before, including biceps, deltoid, supinator longus, latissimus dorsi, pronators,

flexors and extensors of wrist and upper part of pectoralis major on both sides. The triceps, flexors and extensors of thumb and fingers, with all intrinsic hand muscles, are still totally paralysed. The fingers are semi-flexed at the interphalangeal joints; thumbs lightly adducted. The lower limbs are extended at the hips, knees, and ankles. There is distinct wasting of the intrinsic muscles of the hands and of the muscles arising from the internal condyle on both sides, but especially on the right side. The sense of position on passive movement is lost at all points of the little and ring fingers of both hands, being normal in all the other fingers and at the wrists, elbows and shoulders. Upper border of slight anæsthesia on the right hand reaches to web between middle and ring fingers; in the left hand it courses along the long axis of the middle finger (*vide* fig. 3). Owing to "extension" apparatus, limits of anæsthesia on back of trunk cannot now be tested. The tenderness of the skin of the upper part of the chest and root of neck, when patient is being washed, still persists. The supinator-jerk is present and brisk on both sides. The knee-jerks are just present, very faint, mere flickers. No ankle-jerk. Reflex incontinence of urine and fæces as before. Occasional flexor spasms of the lower limbs at hips and knees occur when patient is being moved in bed. Plantar reflexes to-day are both distinctly flexor in type. Healing bed-sores are present on both heels.

October 10.—Patient is discovered to be pregnant. The last catamenial period was about the middle of June.

October 11.—Temperature has gone up to 103·2° F. General bronchitis.

October 14.—Plantars to-day are both extensor in type. Knee-jerks can just be elicited, very faint on both sides. The temperature is up to-day (103°) and respirations are rapid, the chest wall being sucked in at each inspiration.

October 16.—Sense of position tested again to-day; lost in the two ulnar fingers of each hand. In the middle finger of the left hand, which is partially anæsthetic on one side only, the patient sometimes can tell the position of the joints correctly, but occasionally she makes a mistake. She is invariably correct with the middle finger of the right hand.

The pupils are equal in size and react to light. The right pupil was tested with a solution of cocaine and found to dilate well.

To-day, for the first time, she can make a feeble voluntary contraction in the triceps on both sides, but cannot extend either elbow against gravity.

Knee-jerks faint as before. Plantar reflexes both markedly extensor in type. The uterus is enlarged. The patient is apparently about four and a half months pregnant.

The faradic reactions of the arm muscles were tested and found to be as follows:—Normal reactions are present in the deltoid, biceps, supinator longus, and upper part of pectoralis major on both sides, also in the flexors and extensors of wrists (all these muscles can be voluntarily contracted). Normal faradic reactions also are present in the paralysed thenar and hypothenar muscles on both sides.

Diminished reaction to faradism exists in the triceps, lower part of pectoral and interossei on both sides; also in the flexors of the right fingers and the extensors of the right index and right thumb.

There is no reaction to faradism in the common extensors of the fingers or in the flexors of the thumb on either side, nor in the extensors of the left thumb or the flexors of the left fingers. The muscles of the lower limbs react briskly to faradism.

The bronchitis has now cleared up, and the temperature has fallen to 101° F.

October 30.—Patient examined by Dr. Rivers Pollock. Uterus just below umbilicus. Is about twenty-two weeks pregnant. Fœtal heart heard.

November 3.—To-day patient can extend both elbows feeble against gravity, the right better than the left. Pronation and supination are good on both sides; so also are flexion and dorsi-flexion of both wrists. No movement whatever in the fingers of either hand. Atrophy of interossei, thenar, and hypothenar eminences and of muscles arising from the internal condyle on both sides. Both latissimi dorsi contract normally, also the clavicular head of pectoralis major on both sides.

Respirations are rapid, 42 per minute, and the trapezii and sterno-mastoids contract at each inspiration, whilst at the same time the anterior chest-wall becomes retracted. Copious rhonchi are heard all over the chest. Pulse 88, temperature normal.

Anæsthesia exactly the same as before. Tenderness of skin of shoulders and over manubrium sterni still present during washing. Loss of sense of position in two ulnar fingers of right hand and in three ulnar fingers on the left side.

The lower limbs are now semi-flexed at the hips and knees, with strong tonic adductor spasm. The knee-jerks are now brisk, but there is no ankle clonus. The plantar reflexes are extensor in type; the abdominal reflexes are absent. There is a

deep bed-sore on the right gluteal region and superficial sores on both heels, although the patient has been on a water-bed ever since admission.

The pupils are equal in size (3 mm.); they react normally to light and dilate when shaded.

November 6.—General bronchitis. Temperature normal.

November 11.—Anæsthesia and motor paralysis as before. Knee-jerks brisk on both sides. No ankle clonus. Plantar reflexes extensor in type. Temperature 96·8°, pulse 94, respirations 33.

November 14.—Patient died at 6 a.m. from failure of respiration, which became somewhat accelerated (46) at the end, sixty-eight days after the original accident. Temperature at death 96·2° F.

Autopsy (eight hours after death).

When the body was turned on its face, the forward displacement of the fifth cervical vertebra was very evident, rendering the spines of the sixth and seventh vertebræ abnormally prominent.

The brain when removed showed no abnormality on naked-eye examination.

On opening the spinal canal no extra-dural hæmorrhage could be seen at any point. At the level of compression in the lower cervical region the dura was firmly adherent to the bones both in front and behind. At that level the theca was much flattened for a vertical extent of about 2½ cm., the flattened part being distinctly paler than the portions above or below.

On opening the spinal dura mater, the cord was found to be extremely thinned at the level of the upper part of the seventh cervical segment, being reduced to a mere ribbon with an antero-posterior diameter of only 1 mm. at its thinnest part.

The cord, medulla, and pons were placed in 10 per cent. formalin for microscopic examination. Sections were stained by the Marchi and Nissl methods and also with Delafield's hæmatoxylin and van Gieson's picric acid and fuchsin.

The degenerations found in the cord, medulla and pons are described by one of us in another paper.

There was no fracture whatever of the articular processes nor of any portion of either vertebra. The case was therefore one of pure dislocation.

The uterus reached to the umbilicus and contained a female fœtus apparently between the fifth and sixth month of gestation.

Remarks by Mr. William Turner.

There is no doubt that this is a case of complete dislocation of the one vertebra on the other. This accident is comparatively rare as compared with fracture-dislocation, and is only possible in the neck. The inter-vertebral disc was broken, but the articular processes and laminæ of the vertebræ were quite uninjured. When the patient was first seen we could not diagnose any displacement, although it was very carefully looked for, and I fancy this must have been due to the partial slipping back of the bones into position again directly after the accident.

The spine of the fifth vertebra is always slightly depressed, and not so easy to feel as the others in the neck, and this, I think, makes the diagnosis of slight displacement more difficult still. The reasons why no operation was performed at first were that the condition of the patient showed quite definitely that the medulla of the spinal cord was at that time seriously injured, and this made the prognosis hopeless as regards cure from the first, and also the site of the injury. The operation at first contemplated was that of laminectomy. When, however, the fact was evident that dislocation had occurred, and that the position of the bones was far from satisfactory, we decided to try and reduce by means of extension in the hope that some good might perhaps accrue.

On admission she complained of some pain on the lower part of the neck, but there was no tenderness or prominence or depression in the region of any of the cervical spines. The seventh was quite distinct, and the others could be traced up in a middle line from it. There was no bruising in this region, and she had no pain radiating along the distribution of any of the nerve-roots.

The neck muscles were slightly more rigid than usual, and forcible movement of the head caused some pain, but this was quite indefinitely localised. Nine days after the accident it was noticed that the sixth cervical spine could be more distinctly felt than the fifth, and that it was on a distinctly posterior plane, and it was then decided that

a skiagram should be taken from the side to confirm if possible the opinion that the condition was probably due to a dislocation or fracture-dislocation. The accompanying plate shows the result. It was taken by J. H. Montague, of 101, New Bond Street.

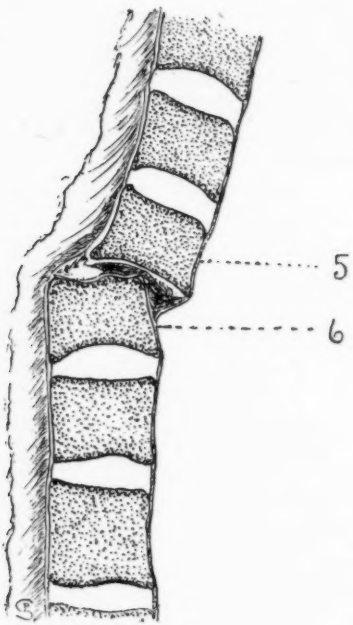

FIG. 4.

Vertical mesial section through dislocation (*natural size*).

The anæsthetic given was A.C.E., and the patient took it as easily as if she were quite well. Almost directly that I put extension on the head, standing at the head of the table, and with my thumbs on the transverse processes of the upper vertebræ, the bone slipped back into position with a distinct jerk, and did not appear to have any tendency to resume the abnormal position. A second photo-

graph was taken by the X-rays two days after the operation, and showed that the displacement had been successfully reduced.

September 21.—The extension apparatus caused the patient a good deal of discomfort and pain in the neck, but not sufficient to discontinue its use. The level of the spinous processes is now normal. The weights extending the head were day by day gradually diminished, as the pain seemed to be more marked, and on October 16 only two pounds was used. It was then noticed that the position of the spinous processes was not quite so good as at the commencement of the extension treatment, and on November 10 there was no doubt that there was again some slight subluxation of the fifth vertebra on the sixth. This was verified on *post-mortem* examination, as may be seen from the drawing of a vertical mesial section through the bones.

Remarks by Dr. Purves Stewart.

The upward limit of the cord lesion, viz., in the upper part of the seventh cervical segment, was determined without much difficulty by the symptoms, motor and sensory. And this diagnosis was verified by the X-ray photographs, which showed with great clearness a displacement of the fifth vertebra forwards on the sixth, a vertebral dislocation which corresponds to a lesion in the cord between the sixth and seventh segments.

Another question was as to the amount of injury to the cord, whether total or partial. The complete paralysis of motion and sensation indicated that both the motor and the sensory paths were interrupted, whilst the wasting of muscles at the level of the lesion and their changed electrical reactions showed that the anterior cornual cells were destroyed at the site of the lesion. The absence of the knee-jerks during the first fortnight after the injury led one at the outset to suppose that the lesion was a complete transverse one. Fourteen days after the injury, however, the knee-jerks reappeared, though excessively faint, and thus led one for the first time

to think that, according to Bastian's dictum,[1] there must still be some slight connection between the parts of the cord above and below the lesion. Such afterwards proved to be the case, although the band of uniting tissue measured only 1 mm. in antero-posterior thickness.

From the fourteenth until the fortieth day the knee-jerks remained excessively faint, so much so that Dr. Hughlings Jackson, who kindly saw the patient on the fortieth day, considered that, being mere flickers, they might practically be taken as absent. On the forty-seventh day, however, the knee-jerks became normal in excitability, and remained so until the patient's death on the sixty-eighth day. At no time were the knee-jerks exaggerated, nor could ankle clonus be obtained at any time.

The absence of knee-jerks for fourteen days, their reappearance and gradual return to normal without the development of ankle clonus up to the time of death, are all very instructive. Sir William Gowers, in the latest edition of his text-book,[2] still maintains, in opposition to Dr. Bastian and others, that after an acute lesion of the cord the knee-jerks may be abolished, but only for a few hours, in consequence of "inhibitory shock," but that if the lumbar centres are intact, they soon return.

In the above case, however, whilst the knee-jerks were absent for two weeks, the plantar reflexes were always elicited with ease, and it is difficult to assume that "inhibitory shock" should abolish the deep reflexes whilst the superficial reflexes survive. Two weeks seems an unusually long time for mere "shock" to cause absence of reflexes. Moreover, the constant presence of the plantar reflexes shows that the spinal centres below the lesion were still capable of excitation. Sir W. Gowers's further contention that absence of the knee-jerks for more than a few hours indicates a "parenchymatous inflammation," or descending myelitis, is not supported by our case. No such inflammation was found in the dorsal or lumbar regions, and the cells of the gray matter in those regions, on examination by the Nissl method, showed no abnormality.

The plantar reflexes were examined within a few hours

after the injury and showed marked extension of the hallux instead of the normal flexor response. At no time were the plantar reflexes absent. This is in complete accordance with the observations of Babinski,[3] subsequently corroborated by van Gehuchten,[4] Collier,[5] and many others. On the nineteenth day, however, both plantar reflexes were distinctly flexor in type, but ever afterwards they invariably gave an extensor response. The significance of the exception is not clear. It shows, however, that whilst in lesions of the pyramidal tract it is the rule to have an extensor plantar reflex, yet exceptionally a flexor response may be temporarily present. The abdominal reflexes could never be elicited at any time during the accident.

The superficial anal reflex, got by pricking the skin of the perineum, was investigated on the twelfth day after the injury and found to be quite brisk, whilst the internal anal sphincter was quite lax and did not grasp the examining finger. Evidently the internal anal reflex is not to be classed physiologically along with the superficial anal reflex, since the former (non-striped muscle) may be paralysed, whilst the latter (striped muscle) survives. I have seen a similar loss of the internal anal reflex with preservation of the superficial anal reflex in a case of acute dorsal myelitis with flaccid paralysis of the lower limbs, the knee-jerks remaining normal; and, again, in a case of tabes with anæsthesia of the lumbar and sacral roots. I am not aware that this "dissociated paralysis" of the internal anal sphincter has hitherto been pointed out.

The last reflex to which we shall refer is the cilio-spinal reflex. Although the lesion was above the point of emergence of the rami communicantes to the cervical sympathetic, yet the sympathetic on the thirty-seventh day still retained its excitability to cocaine. Evidently, therefore, no degeneration had occurred in the pupil-dilating fibres of the sympathetic. The only explanation which seems to offer itself, is that the pupil-dilating fibres traversed the narrow band of tissue uniting the upper and lower portions of the cord without interruption, for, as we see, the lesion was not anatomically quite a complete one.

The muscular paralysis in this case is of special importance from the point of spinal localisation. The focal lesion was one of the seventh cervical segment, and the anterior roots of the seventh segment were the only ones which were afterwards found to be degenerated. Any muscles, therefore, which retained their voluntary motor power with unaltered electrical excitability must be innervated from segments of the cord above the seventh cervical, whilst of the muscles that remained paralysed, those whose faradic excitability was lost or diminished must be innervated from the destroyed seventh segment, and those with normal faradic excitability must be innervated from the eighth cervical or from segments below it. It must also be borne in mind that some muscles are represented in more than one segment of the cord, their motor nuclei in the anterior cornua having a considerable vertical extent.

The following table of muscles, classified on the above principles, is instructive :—

Deltoid Supinator Longus Biceps Pronators Supinators Clavicular part of Pectoralis Major Latissimus Dorsi Extensors of Wrist Flexors of Wrist	Not paralysed, and with normal faradic reactions	*Above* seventh cervical segment
Triceps	At first paralysed, afterwards recovered some motor power. Diminished faradic reactions	Seventh cervical segment
Common Extensors of Fingers (both sides) Flexors of Thumbs (both sides) Extensor Indicis, L. Flexors of Fingers, L. Extensors of Thumb, L.	Totally paralysed, with loss of faradic excitability	
Extensor Indicis, R. Flexors of Fingers, R. Extensors of Thumb, R. Sternal part of Pectoralis Major (both sides) Interossei (both sides)	Totally paralysed, with diminution of faradic excitability	
Thenar Muscles Hypothenar Muscles	Totally paralysed, with normal faradic excitability	*Below* seventh cervical segment

Of the above list of muscles there is already considerable evidence to show that the deltoid, supinator longus and biceps (together with the rhomboids and supra- and infra-spinatus) are innervated chiefly from the fifth cervical segment. The present case has no bearing upon the distribution of the fifth segment, but so far as the sixth and seventh segments are concerned, several important points may be deduced.

According to the present views of most writers on this subject, the extensors of the wrist are to be grouped along with the extensors of the fingers at a common level situated one segment higher up in the cord than the spinal nuclei of the flexors of the wrist and flexors of the fingers, which latter are also stated to be associated together in the cord. Thus Gowers[6] gives the segmental supply of those muscles as follows :—

Triceps Extensors of Wrist Extensors of Fingers	= C. 6 and C. 7.
Flexors of Wrist Flexors of Fingers	= C. 7 and C. 8.

and Horsley[7] makes the following arrangement :—

Triceps Extensors of Wrist and Digits	= C. 7.
Flexors of Wrist and Digits	= C. 8.

Kocher,[8] on the other hand, distributes the same muscles as follows :—

Triceps Extensors of Wrist Flexors of Wrist	= C. 7.
Extensors of Fingers Flexors of Fingers	= C. 8.

Thorburn[9] gives the following arrangement :—

Triceps	= C. 6.
Extensors of Wrist	= C. 7.
Flexors of Wrist	= C. 8.

He does not locate the flexors and extensors of the fingers.

Our results are at variance with the statements of all those writers. In the above case the extensors and flexors

of the wrist were unaffected from the outset, whilst the extensors and flexors of the fingers and thumbs were completely paralysed. It is, therefore, beyond doubt that the correct grouping of those muscles is one which places the *extensors and flexors of the wrist together* and *above the seventh cervical segment*, whilst the *extensors and flexors of the fingers and thumbs* are *at the seventh segment.*

Kocher, it is true, places the extensors and flexors of the wrist together at a level one segment higher than the extensors and flexors of the fingers, but he localises the former at the seventh and the latter at the eighth segment, whereas our case shows that such an arrangement is one segment too low, and that the extensors and flexors of the wrist really belong to the sixth cervical segment.

Nextly as to the triceps muscle. Both Horsley and Kocher place that muscle in the seventh cervical segment only, whilst Thorburn places it in the sixth only. Our case, however, shows that since the muscle, after being at first totally paralysed, subsequently regained part of its motor power, it is probably represented both in the sixth and seventh segments.

With regard to the pectoralis major, it is well known that the clavicular and sternal heads are really two distinct muscles. In our case the sternal head was paralysed, whilst the clavicular was unaffected. The sternal head of the pectoral muscle would therefore seem to be innervated from the seventh cervical segment, whilst the clavicular head is supplied by the sixth and probably by the fifth also, as stated by Gowers.

The exact segmental level of the interossei cannot be determined from our case alone. So far as it goes, however, it tends to show that the spinal nucleus of the interossei is somewhat higher than that of the thenar and hypothenar muscles, since the faradic reactions of the interossei were diminished, whilst those of the thenar and hypothenar eminences were unaltered.

To sum up: our case seems to point to the following arrangement being probably the correct one, so far as these particular muscles are concerned :—

Muscles.	*Segments.*
Pectoralis Major :—Clavicular Head	... C. 5 and C. 6.
Latissimus Dorsi Extensors of Wrist Flexors of Wrist	... C. 6.
Triceps	... C. 6 and C. 7 (chiefly C. 7).
Extensors of Fingers Flexors of Fingers Extensors of Thumb Flexors of Thumb Pectoralis Major :—Sternal Head	... C. 7.
Interossei	... Below C. 7.
Thenar and Hypothenar Muscles	... Below Interossei.

The limit of anæsthesia in this case is of interest, inasmuch as it showed considerable variations before settling down to its final boundary, shown in fig. 3. A curious point also was that the upper limit of the absolute anæsthesia, for the first twelve days at least (*vide* figs. 1 and 2), was much lower behind than in front. (After the twelfth day the anæsthesia could no longer be mapped out on the back of the trunk, owing to the extension apparatus applied.) The significance of this is not clear. Whether it might have been due to the non-severance of a certain number of fibres of the posterior columns is open to question. But the anæsthesia was tested with care, and there can be no doubt as to the fact.

It will also be observed, from a comparison of the charts at different dates, that the upper limit of the slight anæsthesia at first corresponded to the seventh segment, whilst the absolute anæsthesia was considerably below that. Eleven days later, the upper border of the slight anæsthesia reached up to the sixth segment, whilst the absolute anæsthesia had mounted to the seventh. The subsidence of the anæsthesia, which occurred later, to the seventh segment, indicates that the temporary increase of anæsthesia above that level was probably due to some vascular or inflammatory change in the sixth segment, which afterwards passed away.

The permanent anæsthesia (*vide* fig. 3) includes within

its limit the two ulnar fingers of each hand. It is important to note that in those fingers alone was there loss of the sense of position on passive movement. This would indicate that in a segmental anæsthesia of the fingers the loss of joint-sense corresponds accurately in distribution with the distribution of the cutaneous anæsthesia. This segmental arrangement of joint-anæsthesia has apparently not been pointed out by previous observers.

The patient's temperature throughout was normal, except during the occasional occurrence of bronchitis, when it became elevated to 103° or 104° F. For five days before death it was persistently subnormal, between 96° and 97° F.

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(3) Babinski. *Semaine Medicale*, Juillet 28, 1898.
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PROCEEDINGS OF THE NEUROLOGICAL SOCIETY OF LONDON.

At a Clinical Meeting held at 11, Chandos Street, W., on Thursday, March 15, 1900, at 8.30 p.m., the following cases were shown :—

Dr. F. E. Batten.—*Case of congenital cerebellar defect.*

D. S., aged 4 years, was brought to the hospital because she could not walk. She was the first and only child, and instruments had been used at her birth. The mother had had no miscarriages, and had been in good health while carrying the child. The child has never had any illness; she did not begin to use her hands till she was 12 months old.

When first seen, early in 1899, she was a well-nourished child with rather a large head. She was unable to walk but could support her weight, and always tended to fall backwards; afterwards, when taught to put her legs forward, she exhibited a markedly incoordinate gait. The knee-jerks were active, there was no rigidity of the legs, there was no ankle-clonus, and the plantar reflex gave a fairly regular extensor response of the great toe. The movements of the arms were also markedly incoordinate. The intelligence was good and the child could speak in a babyish way. She had a good deal of difficulty in swallowing, and, in consequence, had to be fed very slowly. There was no nystagmus and the fundus was normal. The child was again seen in February, 1900, and was practically in the same condition except that the plantar reflex did not now give such a definite extensor response as when the child was first seen. The child's back was quite normal.

Dr. Farquhar Buzzard.—*A case of cerebral diplegia* (under the care of Dr. T. Buzzard at the National Hospital).

A female child, aged 14 months. Parents alive and healthy. The mother has had seven pregnancies, four of which have resulted in miscarriages at or before the fourth month. There are two healthy children and the patient is the result of the sixth pregnancy. No history of nervous disease in family.

Whilst pregnant of this child the mother was quite healthy except for an affection of the throat causing loss of voice during two months. Labour was easy but not precipitate. Child healthy at birth; no acute illness subsequently. A slight deformity of foot was noticed at one month; since then a gradually progressive inability to move all four extremities, with slight difficulty in swallowing and impairment of vision. Marked wasting recently.

Present condition.—Weight, 8 lbs. Microcephalic and undersized. Marked optic atrophy with no definite pathological changes in the retina. Retraction of head and opisthotonos; generalised rigidity with extension of legs and flexion of arms. Feet dorsi-flexed and everted. Fingers flexed.

Dr. Risien Russell.—(1) *Case of functional wryneck, with clonic spasm of the palate.*

Female, aged 30 years, married. Is seven months pregnant. Has previously borne healthy children. Came under observation about seven weeks ago complaining of a clicking noise which had existed in her head since last May. Her head has also been twisted to the right, and drawn backwards; sometimes it has been twisted to the left. Her condition has made her very miserable, the clicking noise has prevented her from sleeping properly, and she has been losing flesh. No family history of nervous disease. No shock or worry preceded development of present condition, which consists in rapid clonic spasm of the palate, which is responsible for the clicking sound complained of, and which can be heard at some distance from the patient; and torticollis, the chin being usually turned to the right, and the head drawn backwards.

(2) *Two cases of Thomsen's disease* (*myotonia congenita*) in a Hebrew brother and sister. No history of similar affection of other members of the family. No known history of nervous affections. The labours were natural; the children were not backward in walking and talking, and they have neither of them been subject to fits.

(*a*) Male, aged 15½ years. Poorly developed for his age. Natural until 5 years old, when present difficulty in performing movements was first noticed. Condition gradually became more pronounced. Always most marked on first getting up in the morning, when movements of arms, as well as those of legs, are hampered by stiffness of the muscles. As successive movements are performed the stiffness becomes less and less marked. During

the day the difficulty is chiefly noticed in the inferior extremities, progression being hampered by the stiffness which always comes on when movements are first attempted after a period of rest, and which are the more pronounced the longer the preceding period of inactivity. In him, as in his sister, the difficulty is best seen on attempting to mount a flight of stairs, the feat becoming more and more easy as they near the top. On closing the eyes tightly he has difficulty in opening them again, and after he flexes his fingers he can only relax the grasp slowly, in that the persisting contraction of the flexors prevents the full effect of the action of the extensors from being immediately realised. On withdrawing the tongue into the mouth after it has been protruded he experiences a stiff feeling in the organ. There is no permanent spasticity, and the tendon-jerks are natural. Tested by moderate currents the muscles show no notable alteration of the electrical reactions except that with galvanism A.C.C. is as readily obtained as K.C.C.

(*b*) Female, aged 5½ years. Natural development. Phenomena similar, but less marked than in her brother. The condition was first noticed about the age of 4 years, and now, sixteen months since that time, is more pronounced than when she first came under observation about four months ago. The resulting stiffness is less marked than in her brother, and a longer preceding period of inactivity is required to allow of its becoming manifest on attempts at movement.

Dr. Edwin Bramwell.—*Two cases of myasthenia gravis* (under the care of Dr. T. Buzzard at the National Hospital).

(I.) Male, aged 40, schoolmaster. Illness began seven years ago with weakness in fingers of right hand; later, nasal voice, ptosis, difficulty in swallowing. Five years ago legs and arms weak, diplopia, difficulty in coughing and mastication, attacks of dyspnœa and palpitation. Fatigue, cold, and mental excitement all increase intensity of symptoms.

State.—Intelligent man, indistinct nasal speech, upper and lower facial weakness on both sides, diplopia, right-sided ptosis, defective upward movement of eyes, external recti weak, pupils react perfectly, jaws easily tired, tongue moves freely, palate movements and reflex action poor. Weakness of neck, arm and leg muscles, no muscular atrophy or fibrillary tremor. Myasthenic reaction present, arm-jerks poor, knee-jerks active, not exhausted by tapping. Sensation, sphincters, urine and other organs healthy.

(II.) Female, aged 24, housemaid. Anæmic for eighteen months. First symptom, weakness in legs one year ago; soon after developed weakness in arms, nasal speech, ptosis, diplopia, difficulty in mastication, coughing and swallowing.

State.—Double ptosis, ocular movements good, nystagmoid movements on lateral deviation, orbiculares palpebrarum very weak, tongue and palate move well but are soon exhausted, extremities weak, no atrophy, myasthenic reaction present, deep reflexes active, sensation and sphincters unaffected.

Dr. JAMES COLLIER.—*A case of muscular atrophy in the upper extremities* (under the care of Dr. Hughlings Jackson at the National Hospital).

A woman, aged 23 years. A very marked family history of tuberculous disease. Weakness and wasting commencing in the hands and spreading to the fore-arms of fifteen months' duration; severe pain in hands running along ulnar borders of both upper extremities of six months' duration; dull pain in lower cervical spine.

Spinal column natural. Great weakness and wasting in the thenar and hypothenar muscles, and complete paralysis of extensors of fingers. Extensors of wrist and the long extensor of the thumb escape. Slight anæsthesia over the eighth cervical and first dorsal root areas. The muscular is slowly progressive. The patient presents no other physical signs.

AT the Pathological Meeting held at 11, Chandos Street, on Thursday, May 10, 1900, the following specimens were shown:—

Dr. WAKELIN BARRATT.—Sub-dural cyst compressing the right hemisphere.

Dr. F. E. BATTEN.—Series of mounted specimens of some of the grosser pathological changes met with in the nervous system.

Dr. ALEXANDER BRUCE.—Tumour of the third ventricle associated with paralysis of conjugate movements of the eyes upwards and downwards, lateral movements being preserved.

Dr. JAMES TAYLOR.—Changes in the nerve-cells of the third and sixth cranial nerves from a case of ophthalmoplegia externa in which there were difficulties in articulation and swallowing.

Dr. J. S. COLLIER.—(1) Bone from a case of leontiasis ossea and photographs of the patient.

(2) The skull from a case of syringo-myelia simulating leontiasis ossea.

(3) Endothelioma of skull.